Briefing Document for the
Anti-Infective Drugs Advisory Committee

2 June 2009

RESTANZA™ (cethromycin) for Treatment of Mild to Moderate Community-Acquired Pneumonia (CAP)

NDA 22-398

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ABECB	Acute bacterial exacerbations of chronic bronchitis
AC	Alveolar cells
ALT	Alanine aminotransferase
APD	Action potential duration
AST	Aspartate aminotransferase
AUC	Area under the concentration curve
AUC_{free}	Area under the concentration curve for unbound drug
AV	Atrial-ventricular
BID	Twice daily
BLNAR	β-lactamase negative, ampicillin resistance
BMI	Body mass index
BUN	Blood urea nitrogen
CA-MRSA	Community-acquired methicillin-resistant *S. aureus*
CAP	Community-acquired pneumonia
CI	Confidence interval
C_{max}	Maximum serum concentration
$C_{max\ free}$	Maximum serum concentration for unbound drug
CV	Coefficient of variation
ECG	Electrocardiogram
ED	Effective dose
ELF	Extracellular lavage fluid
erm	Erythromycin Resistance Methylase
FDA	Food and Drug Administration
GGT	Gamma glutamyl transferase
hERG	*Ethe-á-go-go*-related gene
IC	Inhibitory concentration
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
LRTI	Lower respiratory tract infections
M1	N-desmethyl metabolite of cethromycin
MIC	Minimum inhibitory concentration
MIC_{90}	Minimum inhibitory concentration at which 90% of the target organisms are killed
MLS_B	Macrolide-lincosamide-streptogramin B
MRSA	Methicillin-resistant *S. aureus*
MSSA	Methicillin-susceptible *S. aureus*
NOAEL	No observed adverse effect level
NOEL	No observed effect level
PAE	Postantibiotic effect
PCV-7	7-valent protein conjugated pneumococcal vaccine
PISP	Penicillin-intermediate *S. pneumoniae*
PRSP	Penicillin-resistant *S. pneumoniae*

PPb	Per-protocol clinical and bacteriological
PPc	Per-protocol clinical
PSSP	Penicillin-susceptible *S. pneumoniae*
PVL	Panton-Valentine leukocidin
QD	Once daily
QT_C	QT interval corrected for heart rate
QT_CB	QT interval corrected, Bazett method
QT_CF	QT interval corrected, Fridericia method
QT_CI	QT interval corrected, individualized method
SD	Standard deviation
TDD	Total daily dose
TID	Three times daily
ULN	Upper limit of normal
USA	United States of America
WBC	White blood cell count

1. EXECUTIVE SUMMARY

1.1. Introduction

Lower respiratory tract infections (LRTI) are the major cause of death globally and the major cause of death due to infectious diseases in the United States of America (USA).[1] Pneumonia is the sixth most common cause of death in the USA. Community-acquired pneumonia (CAP) is commonly defined as an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection, accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and/or localized rales), and occurs in a subject who is not hospitalized or residing in a long-term-care facility for ≥14 days before the onset of symptoms.[1,2]

The rapid and extensive emergence of antibiotic resistant bacteria has resulted in a need to discover new and effective antibiotics that have activity against these pathogens. Currently, the widely used broad spectrum antibiotics include the penicillins, cephalosporins, quinolones, and newer macrolides (roxithromycin, azithromycin, and clarithromycin); however, the emergence of bacterial resistance to these and other antimicrobial agents is becoming a worldwide health problem.[3,4,5,6,7,8]

Clarithromycin derivates, known as the ketolides, were designed particularly to eradicate respiratory pathogens that have acquired resistance to macrolides. *In vitro*, they have a very low potential to select for resistant strains and, unlike existing macrolides, do not induce macrolide-lincosamide-streptogramin B (MLS_B) resistance. Ketolides have consistently exhibited concentration-dependent killing.

Telithromycin (Ketek®) is currently the only drug of the ketolide antibiotic class to obtain Food and Drug Administration (FDA) approval. However, safety concerns including hepatotoxicity, myasthenia gravis exacerbation, loss of consciousness/fainting, and visual disturbances were increasingly reported in the literature following approval.

Cethromycin is a new ketolide with potent activity against Gram-positive, fastidious Gram-negative and atypical bacterial CAP pathogens. The compound also demonstrates activity against penicillin-, macrolide-, and fluoroquinolone-resistant Gram-positive bacteria. It is structurally different from telithromycin in both the nature of the side chain and the position at which the side chain is attached. Cethromycin has been shown to be more active than telithromycin *in vitro* against *S. pneumoniae*, including macrolide-resistant strains containing macrolide efflux, ribosomal methylase or ribosomal mutations. The proposed indication for cethromycin is the treatment of mild to moderate CAP due to strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus, Moraxella catarrhalis*, *Chlamydia pneumoniae*, *Legionella pneumophila*, or *Mycoplasma pneumoniae* in patients 18 years old and above. The recommended oral dose of cethromycin is 300 mg once a day.

1.2. Microbiology

Extensive clinical use of macrolides has resulted in the rapid emergence of macrolide resistance in staphylococci, streptococci, and enterococci. By 2005, 29.5% of *S. pneumoniae* isolated in the USA were found to be non-susceptible to macrolides.[9] Many macrolide-resistant organisms are

also resistant to β-lactams and other antimicrobial classes, thereby limiting treatment alternatives for orally administered agents.

Cethromycin is a potent ketolide antibacterial agent that has been specifically engineered to overcome macrolide resistance and thus provides a new agent in the armamentarium of 21st century physicians to defend public health. The *in vitro* antibacterial activity of cethromycin is more potent than clarithromycin and azithromycin against Gram-positive bacteria. Key elements of this increased potency include:

- Inhibition of protein synthesis through binding to the ribosomal 50S subunit.
- Inhibition of ribosomal 50S subunit formation.
- Strong interactions with 23S rRNA in domains II, IV, and V.
- More rapid cellular uptake than erythromycin.

Data from a broad array of worldwide preclinical susceptibility studies has demonstrated that cethromycin has excellent *in vitro* activity against the key organisms responsible for CAP as evidenced by:

- Activity against *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila.*
- Activity against *S. pneumoniae* isolates resistant to penicillin, macrolides, and fluoroquinolones.
- Inhibition of erythromycin-resistant *S. pneumoniae* strains, including *ermB*, *mefA*, *mefE*, and selected ribosomal mutations.
- Low minimum inhibitory concentration values (MIC) for *S. pneumoniae* strains resistant to tetracycline, trimethoprim-sulfamethoxazole, and second- or third-generation cephalosporins.
- Activity against the USA300 strain of community-acquired methicillin-resistant *S. aureus* (CA-MRSA), which is highly resistant to all macrolides including erythromycin, azithromycin, and clarithromycin.
- Low potential to select for resistant strains.
- No induction of 23S ribosomal RNA methylation or MLS_B resistance.
- Activity against *S. pneumoniae* serotype 19A strains which have resulted from the widespread use of the 7-valent protein conjugated pneumococcal vaccine (PCV-7).

A recent report described eight *S. pneumoniae* clinical isolates obtained from a surveillance program that exhibited reduced susceptibility (MIC range 2 - >64 μg/mL) to telithromycin.[10] For six of the isolates, the cethromycin MIC was at least 8-fold lower than that of telithromycin.

In addition, cethromycin demonstrated *in vivo* efficacy equal or superior to available clinical therapies in animal studies against the most prevalent respiratory pathogens, including *S. pneumoniae* and *H. influenzae*. Animal studies included:

- Lethal systemic infection of mice with:

- *S. aureus* and *S. pneumoniae.*
- Macrolide-sensitive *S. pneumoniae* that were either penicillin-susceptible or penicillin-resistant.
- Macrolide-resistant *S. pneumoniae* that were either penicillin-susceptible or penicillin-resistant.

- Pulmonary infection of mice and rats with *S. pneumoniae* or *H. influenzae.*

The results of *in vivo* animal model efficacy studies, together with excellent *in vitro* activity, indicate that cethromycin would be effective for the treatment of respiratory tract infections including CAP.

1.3. Nonclinical Pharmacology and Toxicology

Nonclinical pharmacology studies evaluated the effect of cethromycin on the central nervous system, pulmonary system, cardiovascular system, and gastrointestinal system.

The toxicity profile of cethromycin has been investigated in rats and monkeys after repeated oral dosing of two weeks, one month, and three months duration. Most of these studies included measures of toxicokinetics and reversibility of the changes was assessed after 1- and 3-month dosing. In addition, reproductive toxicity studies were carried out in rats and rabbits. Cethromycin was also tested for genotoxicity in a standard battery of tests.

Cethromycin was evaluated for potential central nervous system effects in tests of locomotor activity, motor coordination, hypnotic potentiation, proconvulsant/anticonvulsant activity, and nociception in mice and rats. The mild findings in mice and rats were not considered to be toxicologically significant.

The pulmonary safety profile of orally administered cethromycin was assessed in conscious rats. The data demonstrated that cethromycin did not substantially affect pulmonary function at doses up to 180 mg/kg.

Additional key findings in the nonclinical studies included:

- Minor QT prolongation in conscious dogs at free plasma levels of 2.12 µg/mL or 70-fold above the mean human free plasma maximum concentration (C_{max}) at a dose of 300 mg once daily (QD). The mechanism for prolonging QT interval is through inhibition of the I_{Kr} current. The cethromycin 50% inhibitory concentration (IC_{50}) in the hERG assay was 22.1 ± 0.8 µg/mL (28.9 ± 1.0 µM).
- No direct effect of cethromycin was observed on guinea pig ileum smooth muscle; however, contraction was seen in rabbit duodenum smooth muscle with half-maximum contraction occurring at 31.6 µM (24.2µg/ml). Cethromycin was also shown to accelerate gastric emptying and propulsion time in mice, and emesis and loose stools/diarrhea were reported in dog and monkey toxicology studies.
- Cethromycin was acutely toxic in single doses only at highly exaggerated doses in mice and rats.
- No cethromycin-related liver effects were observed in rats and monkeys in 2-week oral toxicity studies up to doses that exceeded the maximum tolerated dose. Mild, reversible

hepatic effects (i.e., increased liver weight, microscopic findings indicative of phospholipidosis, and or mildly increased serum concentration of liver-specific enzymes) were observed in the one-month toxicology studies in rats at 60 mg/kg/day and in monkeys at 70 mg/kg/day. Findings indicative of phospholipidosis, and minimal bile duct effects, were seen in rats at 20 mg/kg in the three month study. There were no liver effects in the monkey three month study at 25 mg/kg/day.

- Cethromycin was not genotoxic in either *in vitro* or i*n vivo* studies. There was no evidence of cethromycin-related teratogenicity in rats or rabbits at maternotoxic doses.
- Testicular atrophy/degeneration and spermatid degeneration were observed in rats but not monkeys. The rat findings occurred in studies of 4-week duration or longer, and were seen at exposure margins of 37-fold (4 weeks) and 31-fold (13 weeks), with no observed adverse effect levels (NOAELs) at 59-fold (2 weeks), 16-fold (4 weeks), and 8-fold (13 weeks). There was a decrease in reproductive outcome from male rats attributed to these changes with an NOAEL for reproductive effects set at a 4-fold margin.

1.4. Clinical Pharmacokinetics

The observed pharmacokinetic profile of cethromycin demonstrated that:

- Peak plasma concentrations for the 300 mg dose were observed at a median of 2 to 3 hours for both cethromycin and the primary metabolite. The half-life for the parent was approximately 5 to 6 hours, and that for the metabolite was approximately 7 to 8 hours.
- No dose adjustments were indicated on the basis of body weight, gender, or race alone.
- No dose adjustments were indicated on the basis of mild or moderate hepatic impairment and renal impairment.
- Food did not have a significant effect on absorption.
- Cethromycin is a CYP3A substrate and has been shown to have inhibitory effects on CYP3A activity *in vitro*. Cautious use of cethromycin is recommended with other drugs that are CYP3A inhibitors, inducers, or substrates.
- No significant inhibitory or inductive effects were observed on CYP1A2, CYP2C19, CYP2D6, or CYP2E1 activity in *in vitro* studies.
- Coadministration with warfarin resulted in a 17% increase in S-warfarin, a CYP2C9 substrate. Given the narrow and variable therapeutic index of warfarin, coagulation tests should be monitored more closely in patients taking concomitant warfarin and cethromycin.
- *In vitro*, cethromycin inhibited the P-gp-mediated transport of vinblastine, and plasma exposures to the P-gp substrate, digoxin, were increased by 31% with cethromycin coadministration *in vivo*. Digoxin plasma concentrations should be monitored and doses may need to be lowered when the two medications are administered together.
- No dose adjustment with ranitidine or sucralfate treatment is necessary.

1.5. Efficacy

Two double-blind, randomized, parallel-group studies were conducted to demonstrate the non-inferiority of cethromycin 300 mg QD to clarithromycin 250 mg twice daily (BID). The primary efficacy endpoint for both studies was the clinical cure rate (defined as the percentage of subjects who had a clinical response of "Clinical Cure") at the Test-of-Cure Visit. The primary objective was to demonstrate non-inferiority of cethromycin relative to clarithromycin for the clinical cure rate in both the intent-to-treat (ITT) and clinical per protocol (PPc) populations (co-primary analyses).

Non-inferiority was to have been demonstrated when the lower limit of the two-sided 95% confidence interval (CI) for the difference in the clinical cure rate at the Test-of-Cure Visit between treatment groups (cethromycin – clarithromycin) was greater than delta, and included zero, for both the PPc and ITT analyses. Delta was determined by the highest clinical cure rate between the cethromycin treatment group and the clarithromycin treatment group, as follows:

Highest cure rate:	**Delta:**
Greater than or equal to 90%	-10%
Greater than or equal to 80% and less than 90%	-15%
Greater than or equal to 70% and less than 80%	-20%

Study CL05-001 demonstrated the non-inferiority of cethromycin 300 mg QD to clarithromycin 250 mg BID for clinical cure rate with a lower 95.0% confidence bound exceeding -10%. For Study CL06-001, non-inferiority was again demonstrated in the clinical cure rate with lower confidence bounds of -9.1% and -11.9% in the PPc and ITT populations, respectively.

The integrated analysis of combined Studies CL05-001 and CL06-001 met the primary endpoint for clinical cure rate in both the ITT and PPc populations. In the ITT population, the clinical cure rate was 83.0% in the cethromycin group compared with 84.8% in the clarithromycin group. Based on the 84.8% clinical cure rate for clarithromycin being between 80% and 90%, a delta value of -15% or less on the lower bound and greater than zero on the upper bound [95% CI: -6.4%, +2.8%] established non-inferiority. In the PPc population, the clinical cure rate was 92.8% in the cethromycin group compared with 94.9% in the clarithromycin group. Based on the 94.9% clinical cure rate for clarithromycin being ≥90%, a delta value of -10% or less on the lower bound and greater than zero on the upper bound [95% CI: -5.4%, +1.2%] established non-inferiority.

Similar results were observed for bacteriological cure rate, pathogen eradication rate, and radiological success rate. Exploratory analyses of bacteriological data suggested a correlation between clinical cure and bacteriological eradication for the target pathogens in both treatment groups.

An increase in overall clinical cure rate from daily doses of 150 mg to 600 mg was not observed in dose-finding studies. As suggested by *in vitro* results, the clinical cure rate for *H. influenzae* did increase when the dose was increased from 150 mg QD to 300 mg QD.

Clinical cure and bacteriological eradication rates were comparable among cethromycin-treated subjects who had erythromycin-susceptible *S. pneumoniae* isolates and those who had

erythromycin-resistant *S. pneumoniae* isolates. In addition, cethromycin was effective in the treatment of subjects with pneumococcal bacteremia.

In summary, studies CL05-001 and CL06-001, alone and in combination, demonstrate the non-inferiority of cethromycin 300 mg QD to clarithromycin 250 mg BID for clinical cure rate. The single exception of a lower bound less than -10% appears partly due to the atypically high cure rate for this clarithromycin regimen[11] and the treatment group imbalance in the number of subjects with indeterminate results (indeterminate results were considered failures in the efficacy analysis). Therefore, the non-inferiority of cethromycin 300 mg QD to clarithromycin 250 mg BID for treatment of CAP has been demonstrated in two adequate and well-controlled clinical studies.

1.6. Safety

Safety data obtained from 5089 subjects have demonstrated that cethromycin is safe and well tolerated. Across the Phase II/III studies in which 3836 subjects received total daily doses (TDD) of cethromycin of 150 mg, 300 mg, or 600 mg, the treatment-emergent adverse event profile of cethromycin was not unique relative to that of other approved antibacterials. The most commonly reported events included dysgeusia, diarrhea, nausea, and headache. The incidence of dysgeusia tended to be higher for all cethromycin-treated subjects compared with those who received active controls, while the incidences of diarrhea, nausea, and headache were similar between the groups. Incidences of deaths, treatment-emergent serious adverse events, and events that resulted in discontinuation were low and similar between all cethromycin-treated subjects and subjects who received active controls, with no clinically meaningful differences observed with respect to these specific types of events reported in either group.

Clinical laboratory evaluation also documents the safety of cethromycin. Review of the Phase II/III clinical program has shown little evidence of significant laboratory concerns. In general, the incidences of possibly clinically significant hematology, chemistry, and urinalysis values were similar between all subjects who received cethromycin and those who received active controls. Although trends for greater mean increases in alanine aminotransferase (ALT), creatinine, and uric acid were observed among all cethromycin-treated subjects compared to those who received active controls at the final on-therapy visit, no remarkable differences were observed between the groups by the final off-therapy visit. Shifts from normal baseline to the greatest deviation in post-baseline hematology, chemistry, or urinalysis values were similar between all cethromycin-treated subjects and those who received active controls.

Evaluations of vital signs in the Phase II/III clinical program showed no notable differences between subjects who received cethromycin and those who received active controls. A Phase I thorough QT study showed no signal of any effect of cethromycin on atrial-ventricular (AV) conduction, depolarization, or cardiac repolarization as measured by the PR, QRS, individual-corrected QT interval (QT_CI), or Fridericia-corrected QT interval (QT_CF) durations. In addition, no remarkable differences were observed between all cethromycin-treated subjects and those who received active controls in the evaluation of electrocardiogram (ECG) data across the Phase II/III clinical program.

The significant safety concerns, including hepatotoxicity, visual disturbances, loss of consciousness, and exacerbation of myasthenia gravis, observed with the only approved ketolide agent, telithromycin, were not observed in the cethromycin clinical program. Exploratory

analyses were conducted to evaluate all adverse events in the cethromycin safety database with any potential to be associated with these safety concerns. Any identified events were tabulated and compared to results in placebo and active control treated subjects. All events, regardless of treatment groups, were thoroughly investigated for indications of a more serious event. Regarding serious hepatic events, no subject in the cethromycin database met the criteria for Hy's Law, a predictor of liver toxicity. In addition, no events of jaundice, fulminant liver failure, liver biopsy, or liver transplant occurred. In all Phase II/III studies, the incidence of at least one treatment-emergent adverse event related to hepatic function (e.g., ALT increased) was similar between all subjects who received cethromycin and those who received active controls. There was no consistent pattern of higher percentages of subjects in the cethromycin versus active control group shifting from normal baseline in liver function test values to ≥3 × upper limit of normal (ULN) and ≥5 × ULN following treatment. Based on the totality of data, there is no evidence of clinically important liver toxicity associated with cethromycin administration. Among the other adverse events of special interest, the incidences of visual disturbances, loss of consciousness, and exacerbation of myasthenia gravis were similar to that observed in the placebo and active control groups. Events of syncope were slightly elevated in the Phase I studies due to vasovagal events associated with phlebotomy or study procedures.

The treatment-emergent adverse event profile of cethromycin was consistent across demographic characteristics including gender, race, age, region, alcohol use, tobacco use, and Fine criteria. Additionally, no clinically important differences were observed in the incidences of possibly clinically significant laboratory values when analyzed by gender and age. A history of cardiac disease, hepatic disease, or diabetes had no clinically important effect on the treatment-emergent adverse event profile of cethromycin.

1.7. Conclusions

In conclusion, the medical community is faced with additional challenges in the treatment of mild to moderate CAP. New agents must have the capability to eradicate drug-resistant causative pathogens, including new target organisms such as the USA300 strain of community-acquired MRSA and the 19A and 19F serotypes of *S. pneumoniae,* in addition to the susceptible strains of the typical pathogens and the atypical or intracellular pathogens. A satisfactory drug must be able to eradicate all of these species yet leave other non-CAP causative species alone, thus limiting undesirable secondary outcomes, such as the overgrowth of harmful bacteria such as *Clostridium difficile* in the gut. This selective antibacterial activity must coexist with a tolerable and benign safety profile, something which has become increasingly difficult for an antibacterial agent to achieve in the recent past. Several currently available agents lack the antibacterial activity to address the pathogen challenges facing the CAP treatment provider. While several have the antibacterial activity, this activity comes at the expense of collateral damage and patient safety.

Cethromycin provides the prescribing community with an agent that retains the antibacterial profile necessary for the treatment of common and more difficult-to-treat CAP, while maintaining an acceptable safety profile, ensuring that the individual receiving the drug benefits from the treatment. The information from the clinical development program supports the use of cethromycin in the treatment of mild to moderate CAP due to susceptible strains of *S. pneumoniae, H. influenzae, S. aureus, M. catarrhalis, C. pneumoniae, M. pneumoniae,* or

L. pneumophila in patients 18 years of age and older. The recommended dose is 300 mg QD for a total of 7 days. The data in the population examined thus far and presented in this submission support the conclusion that the benefits of cethromycin exceed the risks for the treatment of mild to moderate CAP.

2. INTRODUCTION

2.1. Background for Community-Acquired Pneumonia

Lower respiratory tract infections are the major cause of death globally and the major cause of death due to infectious diseases in the USA.[1] Pneumonia is the sixth most common cause of death in the USA. Community-acquired pneumonia is commonly defined as an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection, accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and/or localized rales), and occurs in a subject who is not hospitalized or residing in a long-term-care facility for ≥14 days before the onset of symptoms.[1,2]

Symptoms of acute LRTI include fever or hypothermia, rigors, sweats, new cough with or without sputum production, change in the color of respiratory secretions in a subject with chronic cough, chest discomfort, wheezing, or the onset of dyspnea. Most clinical studies require the presence of at least two of these symptoms in eligible subjects. Most subjects also have nonspecific symptoms such as fatigue, myalgias, abdominal pain, anorexia, and headache.

The most common etiologic agent identified in virtually all studies of CAP is *Streptococcus pneumoniae*, and this agent accounts for approximately two-thirds of all cases of bacterial pneumonia.[1,12] Other known causative pathogens include *H. influenzae* (most isolates of which are non-type B), *M. pneumoniae*, *C. pneumoniae*, *S. aureus*, *Neisseria meningitidis*, *M. catarrhalis* and other Gram-negative rods, and *L. pneumophila.*[2,12,13,14,15]

Lately, the rapid and extensive emergence of antibiotic resistant bacteria has resulted in a need to discover new and effective antibiotics that have activity against these pathogens. Currently, the widely used broad spectrum antibiotics include the penicillins, cephalosporins, quinolones, and newer macrolides (roxithromycin, azithromycin, and clarithromycin); however, the emergence of bacterial resistance to these and other antimicrobial agents is becoming a worldwide health problem.[3,4,5,6,7,8] Thus, the need to develop better therapeutic regimens warrants rigorous investigative efforts.

2.2. Background for Ketolide Antibiotics

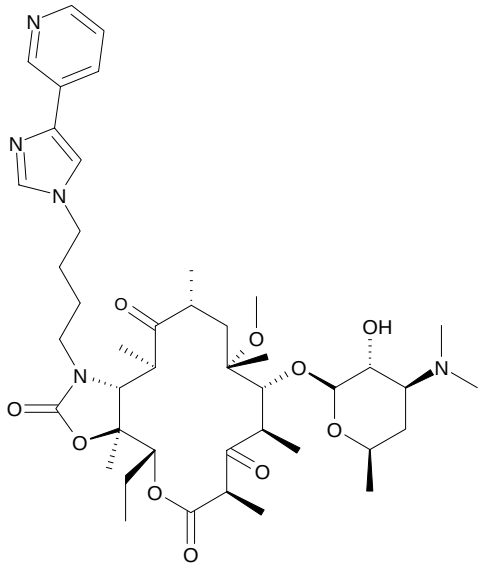
The 3-des-cladinosyl-3-oxo-11,12-cyclic carbamate clarithromycin derivates, known as the ketolides, were designed particularly to eradicate respiratory pathogens that have acquired resistance to macrolides. *In vitro*, ketolides have shown potent activity against common respiratory pathogens, including strains of penicillin-resistant and erythromycin-resistant *S. pneumoniae.*[16,17] They have a very low potential to select for resistant strains and, unlike existing macrolides, do not induce MLS_B resistance. Their pharmacokinetic profile allows for QD dose administration, with extensive tissue distribution relative to serum. Ketolides have consistently exhibited concentration-dependent killing. Given their *in vitro* activity and resistance profile, ketolides are important new drugs for the treatment of a range of community-acquired respiratory tract infections.

Telithromycin (Ketek®) is currently the only drug of the ketolide antibiotic class to obtain FDA approval. It was initially approved in 2004 for the treatment of acute bacterial exacerbations of

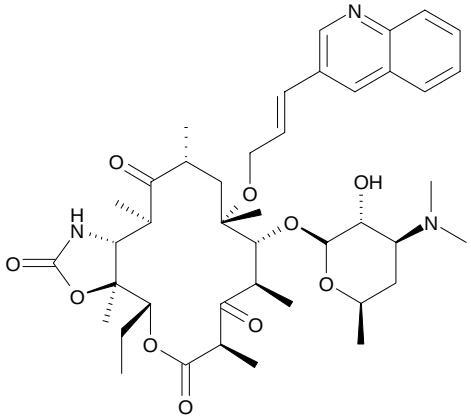
chronic bronchitis (ABECB), bacterial sinusitis, and CAP. However, safety concerns including hepatotoxicity, myasthenia gravis exacerbation, loss of consciousness/fainting, and visual disturbances were increasingly reported in the literature following approval. In 2007, the FDA removed the bacterial sinusitis and ABECB indications, as the balance of benefits and risks did not support the continued approval of telithromycin for these generally non-serious and often self-limited illnesses, but continued to allow the use of telithromycin the treatment of patients with CAP.

Cethromycin is a new ketolide having potent antibacterial activity against Gram-positive, fastidious Gram-negative and atypical bacterial pathogens of CAP, including those resistant to penicillin, macrolides and fluoroquinolones. The antibacterial activity of cethromycin is mediated through binding to the bacterial target, the 23S rRNA of the 50S subunit of the ribosome. Macrolide agents share this target; however, they have fewer contact points and lower binding affinity. Resistance to macrolide agents is often through methylation of the macrolide contact site resulting in an inability to bind to the target. By virtue of additional contact points, cethromycin is able to overcome this methylation-mediated resistance mechanism. In addition, the enhanced binding affinity of cethromycin to its molecular target is helpful in overcoming bacterial resistance mediated via an efflux mechanism and also results in marked increases in antibacterial activity when compared to both macrolide agents and the marketed ketolide agent telithromycin. Cethromycin retains activity against clinical isolates of telithromycin-resistant *S. pneumoniae*, a phenomenon believed to be the result of the enhanced binding kinetics of cethromycin. Unlike existing macrolides, cethromycin does not induce MLS_B resistance and has a very low potential to select for resistant strains.

Cethromycin is structurally different from telithromycin in both the nature of the side chain and the position at which the side chain is attached. Cethromycin has been shown to be more active than telithromycin *in vitro* against *S. pneumoniae*, including macrolide-resistant strains containing macrolide efflux, ribosomal methylase or ribosomal mutations. In animal models, cethromycin has *in vivo* efficacy against the most prevalent respiratory pathogens, including *S. pneumoniae, H. influenzae,* and macrolide- and penicillin-resistant strains of *S. pneumoniae*. Pharmacologic studies suggest that cethromycin penetrates well into pulmonary tissue and intracellular locations, and the clinical trial data demonstrate that cethromycin is effective in the treatment of CAP. In addition, preclinical data and clinical safety data obtained from 5089 subjects dosed in the cethromycin clinical program have not identified the safety concerns associated with telithromycin.



Telithromycin



Cethromycin

Abbott Laboratories discovered cethromycin and conducted the initial development program, which consisted of 36 Phase I and 10 Phase II/III studies, using the designation ABT-773 for cethromycin. In 2005, Advanced Life Sciences licensed cethromycin from Abbott Laboratories. Cethromycin has been developed by Advanced Life Sciences for the treatment of mild to moderate severity CAP due to strains of *S. pneumoniae*, *H. influenzae*, *S. aureus, M. catarrhalis*, *C. pneumoniae*, *L. pneumophila*, or *M. pneumoniae* in patients 18 years old and above. Three additional clinical studies (two Phase III and one Phase I) were conducted by this Sponsor in support of this development program.

2.3. Regulatory History

Upon licensing cethromycin from Abbott Laboratories in 2005, sponsor responsibilities and obligations for IND 57,836 were accepted by Advanced Life Sciences. Regulatory discussions and communications between FDA and Advanced Life Sciences have occurred frequently throughout the cethromycin CAP development program.

On September 30, 2008 Advanced Life Sciences submitted NDA 22-398 for the use of cethromycin in the treatment of mild to moderate CAP in adults. After completion of the filing review, the FDA filed NDA 22-398 on Dec 15, 2008 with a standard review classification and user fee goal date of July 31, 2009.

3. PROPOSED INDICATION

RESTANZA™ is indicated for treatment of mild to moderate CAP due to susceptible strains of *S. pneumoniae*, *H. influenzae*, *S. aureus*, *M. catarrhalis*, *C. pneumoniae*, *M. pneumoniae*, or *L. pneumophila* in patients 18 years of age and older.

4. MICROBIOLOGY

Extensive clinical use of macrolides has resulted in the rapid emergence of macrolide resistance in staphylococci, streptococci, and enterococci. By 2005, 29.5% of *S. pneumoniae* isolated in the USA were found to be non-susceptible to macrolides.[9] Many macrolide-resistant organisms are also resistant to β-lactams and other antimicrobial classes, thereby limiting treatment alternatives for orally administered agents.

Cethromycin is a ketolide antibacterial agent with potent activity against Gram-positive, fastidious Gram-negative and atypical CAP-causative pathogens. The compound also demonstrates activity against penicillin-, macrolide-, and fluoroquinolone-resistant bacteria. The *in vitro* antibacterial activity of cethromycin is more potent than clarithromycin and azithromycin against Gram-positive bacteria. Key elements of this increased potency include:

- Inhibition of protein synthesis through binding to the ribosomal 50S subunit.
- Inhibition of ribosomal 50S subunit formation.
- Strong interactions with 23S rRNA in domains II, IV, and V.
- More rapid cellular uptake than erythromycin.

Data from a broad array of worldwide preclinical susceptibility studies has demonstrated that cethromycin has excellent *in vitro* activity against the key organisms responsible for CAP as evidenced by:

- Activity against *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila.*
- Activity against *S. pneumoniae* isolates resistant to penicillin, macrolides, and fluoroquinolones.
- Inhibition of erythromycin-resistant *S. pneumoniae* strains, including *ermB*, *mefA*, *mefE*, and selected ribosomal mutations.
- Low MIC values for *S. pneumoniae* strains resistant to tetracycline, trimethoprim-sulfamethoxazole, and second- or third-generation cephalosporins.
- Activity against the USA300 strain of CA-MRSA, which is highly resistant to all macrolides including erythromycin, azithromycin, and clarithromycin.
- Low potential to select for resistant strains.
- No induction of 23S ribosomal RNA methylation or MLS_B resistance.
- Activity against *S. pneumoniae* serotype 19A strains which have resulted from the widespread use of the PCV-7 vaccine.

A recent report described eight *S. pneumoniae* clinical isolates obtained from a surveillance program that exhibited reduced susceptibility (MIC range 2 - >64 μg/mL) to telithromycin.[10] For six of the isolates, the cethromycin MIC was at least 8-fold lower than that of telithromycin.

In addition, cethromycin demonstrated *in vivo* efficacy equal or superior to available clinical therapies in animal studies against the most prevalent respiratory pathogens, including *S. pneumoniae* and *H. influenzae*. Animal studies included:

- Lethal systemic infection of mice with:
  - *S. aureus* and *S. pneumoniae.*
  - Macrolide-sensitive *S. pneumoniae* that were either penicillin-susceptible or penicillin–resistant.
  - Macrolide-resistant *S. pneumoniae* that were either penicillin-susceptible or penicillin–resistant.
- Pulmonary infection of mice and rats with *S. pneumoniae* or *H. influenzae*.

The results of *in vivo* animal model efficacy studies, together with excellent *in vitro* activity, indicate that cethromycin would be effective for the treatment of respiratory tract infections including CAP.

4.1. Mechanism of Action

Cethromycin inhibits protein biosynthesis by binding to the 23S ribosomal RNA of the 50S ribosomal subunit of the bacterial ribosome, stimulating the dissociation of peptidyl-tRNA from the ribosome during the translocation process and blocking the peptide exit channel. In addition, cethromycin interacts with partially assembled 50S subunit precursors and prevents the complete formation of bacterial ribosomes. Cethromycin binds to ribosomes much more tightly than erythromycin, and exhibits inhibition of bacterial protein synthesis in both macrolide-susceptible and macrolide-resistant bacteria. Ribosome crystallography studies demonstrated strong interactions of cethromycin with 23S rRNA in domains II, IV and V, consistent with the binding affinity observed for cethromycin.[18] Cethromycin demonstrates good activity against macrolide-resistant pneumococci expressing either *erm* methylases or efflux pumps.

4.1.1 Inhibition of Protein Synthesis

Like macrolides, ketolides such as cethromycin and telithromycin interact with the 50S ribosomal subunit by blocking the peptide exit channel, thereby stalling protein synthesis.[19] Cethromycin has been shown to inhibit protein synthesis in both Gram-positive and Gram-negative bacteria. The addition of cethromycin to actively growing *S. pneumoniae* ATCC 49619 inhibited protein synthesis.[20] The cethromycin inhibitory effect had an apparent IC_{50} value of 0.0025 μg/mL, which is within the range of expected MIC values for macrolide-sensitive *S. pneumoniae*.

Cethromycin is active against *H. influenzae*, exhibiting an MIC_{90} value of 4 μg/mL for macrolide-sensitive clinical isolates. An IC_{50} value of 1.25 μg/mL was observed for both cethromycin and telithromycin inhibition of translation in actively growing *H. influenzae* cells.[21]

4.1.2 Inhibition of Ribosomal 50S Subunit Formation

Macrolides and ketolides have a second mechanism of action involving inhibition of 50S subunit formation. The binding site for macrolides and ketolides is formed on partially assembled 50S subunit particles, and drug binding at this stage leads to inhibition of complete subunit formation.[20]

In *S. pneumoniae* cells, 0.005 ug/ml of cethromycin inhibited 50S particle formation, while 30S particle formation was not inhibited until higher concentrations of cethromycin were present.[20] However, examination of 30S and 50S particle formation in *H. influenzae* cells treated with increasing concentrations of cethromycin revealed a decline in the synthesis of both ribosomal subunits. This led to the conclusion that ketolides have only one target in *H. influenzae* that binds the fully mature 50S particle and inhibits protein synthesis.[21] It was suggested that ketolides are less potent against *H. influenzae* because only one target is present, whereas *S. pneumoniae* cells are inhibited at both the level of protein synthesis and 50S particle formation.

4.1.3 Ribosome Binding

Cethromycin binds approximately 15 times more tightly than erythromycin, and 2 times more tightly than telithromycin, to MLS_B-susceptible ribosomes of *S. pneumoniae*.[22,23] Against *H. influenzae* wild-type ribosomes, cethromycin binding was more than 20-fold greater than that of erythromycin.[24] Kinetic studies have demonstrated that cethromycin associates very rapidly with susceptible ribosomes and dissociates very slowly. The strong and rapid binding of cethromycin to, and slow dissociation from, ribosomes are further supported by ribosomal crystallography studies.[25]

Studies of the interaction of cethromycin with *S. pneumoniae* have shown that the compound reaches high levels within the bacterium much more rapidly than erythromycin. This may, in part, be due to the observation that cethromycin binds to non-methylated ribosomes with 10- to 100-fold higher affinity than either erythromycin or clarithromycin. This high affinity has been shown with ribosomes isolated from both *S. pneumoniae* and *H. influenzae*. Cethromycin is also able to interact with methylated *S. pneumoniae* ribosomes possibly at a second binding site, although with lower affinity than with the primary binding site. The interaction with methylated ribosomes in macrolide-resistant bacteria, together with the much tighter binding to non-methylated ribosomes, confer potent inhibitory properties upon cethromycin against bacteria containing the *ermB* ribosomal methylase. Additionally, unlike macrolides and other ketolides, cethromycin has not been shown to increase levels of methylation in bacteria with lower levels of *ermB* expression.

4.2. Mechanism of Resistance

Clinically relevant macrolide resistance mechanisms primarily include the following: (*i*) the presence of an *erm* gene encoding a methylase enzyme which prevents macrolide binding to the ribosome; (*ii*) the presence of an efflux pump which transports macrolides back out of the cell; and (*iii*) ribosomal mutations in the 23S rRNA of the 50S ribosomal subunit or in the ribosomal proteins L4 or L22.[18,26]

Superposition of the crystal structures of cethromycin, telithromycin, and erythromycin confirm that macrolides and ketolides bind in the same general region of the 23S rRNA present in the 50S ribosomal subunit; however, cethromycin demonstrates additional and stronger interactions in domains II, IV, and V. It is, therefore, not surprising that the presence of one or more of the macrolide resistance mechanisms results in decreased susceptibility to cethromycin, albeit to a lesser extent than macrolides and other ketolides.

Cethromycin retains activity against strains of *S. pneumoniae* that are resistant to macrolides due to an inducible or constitutive *erm* gene that confers resistance to MLS_B drugs (see Section 4.3.1). Mutations in streptococcal rRNA or ribosomal proteins, most likely selected by macrolide exposure, do not typically result in resistance to cethromycin.[23] In addition, cethromycin does not induce higher levels of 23S rRNA methylation, and thus MLS_B resistance, in strains of *S. pneumoniae* and *S. aureus* with an inducible *erm* gene.[22,27]

Cethromycin has been shown to be very active against bacterial strains containing the macrolide efflux protein *mef*(A,E). This suggests that cethromycin, unlike the macrolides, is a poor substrate for this family of efflux pumps and they are not effective at lowering intracellular concentrations of cethromycin. The decreased affinity of the bacterial efflux pump toward cethromycin, coupled with the increased affinity of the drug for bacterial ribosomes, results in the superior activity profile of cethromycin.

Laboratory-derived resistance to cethromycin has been reported. Mutants of *S. pneumoniae* and *S. aureus* mutants were selected less frequently by cethromycin than erythromycin. Interestingly, cethromycin did not select for *H. influenzae* mutants that were resistant to cethromycin.[28]

4.3. *In Vitro* Activity

The antimicrobial spectrum of cethromycin was evaluated against a wide variety of clinical isolates in a large number of studies conducted worldwide. In addition, a recent surveillance study examined cethromycin activity in over 6,000 clinical isolates of Gram-positive and Gram-negative microorganisms collected primarily from 2004 to 2007, mostly from the USA and Europe. Overall, cethromycin demonstrated potent activity against *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*, the key organisms responsible for CAP.

4.3.1 *Streptococcus pneumoniae*

Streptococcus pneumoniae is one of the most common pathogens that cause bacterial CAP. The susceptibility of *S. pneumoniae* to penicillin and macrolide antibiotics has fallen precipitously in recent years. By 2005, 29.5% of *S. pneumoniae* isolated in the USA were found non-susceptible to macrolides.[9] Cethromycin has been specifically engineered to overcome such resistance.

Cethromycin is consistently active against all pneumococci, irrespective of their penicillin-susceptibility. All of the penicillin-nonsusceptible isolates of *S. pneumoniae* studied were inhibited by cethromycin (MICs of $\leq$2.0 μg/mL) (Table 1). In addition, 97% of all penicillin non-susceptible pneumococci were inhibited by cethromycin at a concentration of 0.125 μg/mL, while only 87% of these isolates were inhibited by the same concentration of telithromycin.[29] The cethromycin MIC_{90} value versus *S. pneumoniae* isolates with penicillin MIC values of $\geq$8 μg/mL was 2- to 3-doubling dilutions lower than telithromycin (Table 1).

Table 1: Comparative *In Vitro* Activity of Antibiotics Against Penicillin-Susceptible and -Nonsusceptible *S. pneumoniae*

Penicillin Susceptibility[a] (N)	Cethromycin		Telithromycin		Clarithromycin		Azithromycin		Erythromycin	
	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}
PSSP (1,127)	≤0.008 – 0.5	≤0.008	≤0.0005 – 2	0.008	≤0.03 – >64	≤0.03	≤0.03 – >64	0.12	≤0.03 – >64	0.06
PISP (80)	0.125 – 2	0.125	0.125 – 2	0.125	≤0.008 – >64	>64	0.125 – 128	128	0.125 – 128	128
PRSP (253)	0.125 – 1	0.125	0.125 – 1	0.125	≤0.008 – >64	>64	0.125 – 128	128	0.125 – 128	128
PRSP (MIC ≥8) (20)	0.004 – 0.25	0.12	0.008 – 0.5	0.5	0.03 – >4	>4	0.03 – >4	>4	0.03 – >4	>4

MIC unit: µg/mL; PSSP, penicillin-susceptible *S. pneumoniae*; PISP, penicillin-intermediate *S.* pneumoniae; PRSP, penicillin-resistant *S. pneumoniae*

a The pneumococcal susceptibility to penicillin was assessed using the penicillin breakpoints: ≤0.06 µg/mL, Susceptible; 0.12 – 1, Intermediate; >1, Resistant. In 2008, CLSI revised penicillin breakpoints for non-meningitis isolates: ≤2 µg/mL, Susceptible; 4, Intermediate; ≥8, Resistant.

Cethromycin retains potency against *S. pneumoniae*, regardless of macrolide-susceptibility (Table 2). At a concentration of 0.125 μg/mL, cethromycin inhibited 100% of erythromycin-susceptible and 97% of erythromycin-nonsusceptible *S. pneumoniae* isolates. Comparatively, telithromycin inhibited 83% of erythromycin-nonsusceptible isolates at this concentration.[29]

Cethromycin is generally 1 to 2 doubling dilutions more active than telithromycin against macrolide-susceptible streptococci. The improved activity of cethromycin compared to that of telithromycin is even more evident when examining MIC values against pneumococci with defined macrolide-resistance mutations such as efflux *mef*(A,E), methylase *erm*B, or a combination of efflux and methylase (e.g., *erm*B/*mef*A and *erm*B/*mef*E).[23,27,30,31] The activity of ketolides against *S. pneumoniae* isolates carrying both *erm*B and *mef*A is very significant, as this genotype exhibited multidrug resistance and its prevalence increased from 9.7% to 18.4% between 2000 – 2004 in the USA.[32]

Table 2: Comparative *In Vitro* Activity of Antibiotics Against Macrolide-Susceptible and -Resistant *S. pneumoniae*

Macrolide Phenotype (N)	Cethromycin		Telithromycin		Clarithromycin		Azithromycin		Erythromycin	
	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}
Ery-S (30)	≤0.001 – 0.008	0.004	≤0.008 – 0.03	0.015	0.002 – 0.06	0.03	0.004 – 0.25	0.12	0.002 – 0.06	0.03
*mef*A (23)	≤0.002 – 0.12	0.06	0.015 – 2	1	0.5 – 8	4	2 – 16	8	2 – 8	8
*mef*E (100)	≤0.008 – 0.25	0.125	≤0.008 – 1	0.5	4 – >128	32	2 – 32	16	2 – 32	16
*erm*B (150)	0.008 – 2	0.25	0.008 – 8	0.5	2 – >128	>128	4 – >128	>128	2 – >128	>128
*erm*B/*mef*A (39)	≤0.002 – 0.5	0.25	≤0.002 – 0.5	0.25	------	------	------	------	0.5 – >128	>128
*erm*B/*mef*E (8)	≤0.008 – 0.5	0.5	≤0.008 – 1	1	>128	>128	>128	>128	>128	>128
Ribosomal mutation (19)	≤0.008 – 1	0.12	≤0.008 – 0.5	0.12	4 – 64	32	>64	>64	0.06 – >128	>128

MIC unit: μg/mL; Ery-S, erythromycin-susceptible

Emerging resistance to the fluoroquinolones is also of concern. Cethromycin demonstrated an MIC_{90} of 0.03 µg/mL against 31 clinical isolates of fluoroquinolone-resistant pneumococci with a characterized resistance mechanism (efflux and topoisomerase II) (Table 3).[33]

Table 3: Comparative *In Vitro* Activity of Antibiotics Against Fluoroquinolone-Susceptible and -Resistant *S. pneumoniae*

Fluoroquinolone Phenotype (N)	Antimicrobial	MIC Range	MIC_{50}	MIC_{90}
Fluoro-S (31)	Cethromycin	≤0.004 –0.25	≤0.004	0.06
	Levofloxacin	1 – 2	1	2
	Trovafloxacin	0.03 – 0.12	0.12	0.12
	Ciprofloxacin	1 – 4	2	2
90% *gyrA* and *parC;* 10% *parC* (31)	Cethromycin	≤0.004 – 0.25	≤0.004	0.03
	Levofloxacin	0.5 - 32	16	32
	Trovafloxacin	0.06 - 8	2	4
	Ciprofloxacin	0.5 - 64	32	64

MIC unit: µg/mL; Fluoro-S, fluoroquinolone-susceptible

Furthermore, cethromycin displayed potent activity against *S. pneumoniae* strains resistant to tetracycline, trimethoprim-sulfamethoxazole, and ciprofloxacin with MIC_{90} values of 0.06 µg/mL (Table 1).[30]

Table 4: Comparative *In Vitro* Activity of Antibiotics Against *S. pneumoniae* Resistant to Other Classes of Antibiotics

Resistant Phenotype (N)	Cethromycin		Telithromycin		Clarithromycin		Azithromycin		Erythromycin	
	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}
Tet-R tet(M) (200)	≤0.004 – 0.25	0.06	0.002 – 0.5	0.12	≤0.004 – 2	0.5	≤0.004 – 4	1	≤0.004 – 2	0.5
TMP/SMZ-R (50)	≤0.004 – 0.12	0.06	0.002 – 0.5	0.12	≤0.004 – 1	0.5	≤0.004 – 4	0.5	≤0.004 – 1	0.5
Ciprofloxacin MIC >4 µg/mL (100)	0.004 – 0.06	0.06	0.015 – 0.5	0.12	≤0.004 – 2	0.5	≤0.004 – 4	1	≤0.004 – 2	0.5

MIC unit: µg/mL; Tet-R Tet(M), tetracycline-resistant strains with defined tetM mutation; TMP/SMZ-R, trimethoprim/sulfamethoxazole-resistant

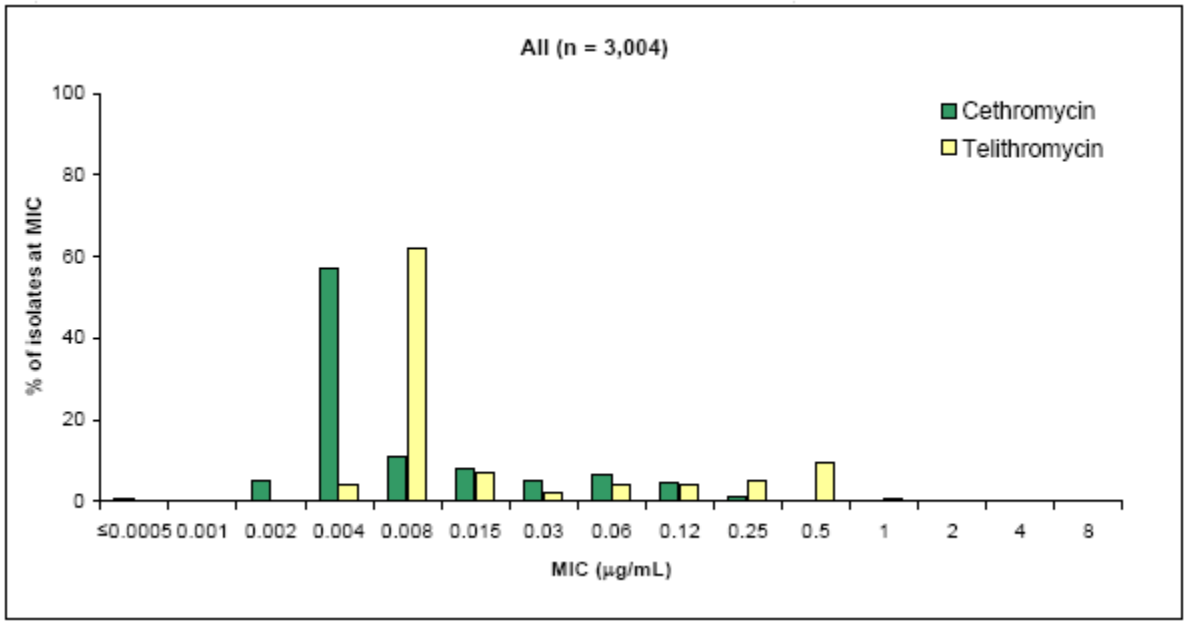
Although reported telithromycin resistance is rare, a recent report by Eiznhamer *et al*., described eight *S. pneumoniae* clinical isolates obtained from a surveillance program that exhibited reduced susceptibility (MIC range 2 - >64 µg/mL) to telithromycin.[10] Table 5 shows that the isolates were all highly resistant to erythromycin, with MIC values of >128 µg/mL. Interestingly, for 6 of the isolates, the cethromycin MIC was at least 8-fold lower than that of telithromycin. One isolate had identical 2 µg/mL MIC values for the two ketolides, while for one isolate telithromycin was one doubling dilution lower than cethromycin. Polymerase chain reaction amplification revealed that all eight strains were positive for *ermB*, and all but one were negative for *mefA*.

Table 5: Susceptibility of Cethromycin to Eight Telithromycin-Nonsusceptible *S. pneumoniae* Clinical Isolates from the USA

Strain	MIC (µg/mL)			Telithromycin:Cethromycin MIC Ratio
	Cethromycin	Telithromycin	Erythromycin	
ATCC 49619	0.015	0.03	0.12	2
1153335	4	2	>128	0.5
1159283	0.5	4	>128	8
1198617	2	2	>128	1
1353545	2	16	>128	8
1353676	2	16	>128	8
1356798	0.25	8	>128	32
1431711	0.5	>64	>128	>128
1473386	0.5	8	>128	16

The potent *in vitro* activity of cethromycin was recently confirmed against over 3,000 clinical *S. pneumoniae* isolates collected in the USA and Europe from 2004 to 2007. The MIC distribution for cethromycin and telithromycin is shown in Figure 1.

Figure 1: MIC Distribution for Cethromycin and Telithromycin for *S. pneumoniae*: USA and Europe



4.3.2 *Haemophilus influenzae*

Haemophilus influenzae is also one of the most common causative pathogens in CAP. The prevalence of ampicillin-resistant *H. influenzae* due to β-lactamase production among the nontypable strains is very high, and resistance to β-lactams due to modification of penicillin-binding proteins [β-lactamase-negative, ampicillin-resistant (BLNAR)] has also been reported. Cethromycin retained *in vitro* activity against *H. influenzae* that was similar to that of azithromycin and telithromycin but 4-fold more potent than erythromycin and clarithromycin (Table 6).[34,35]

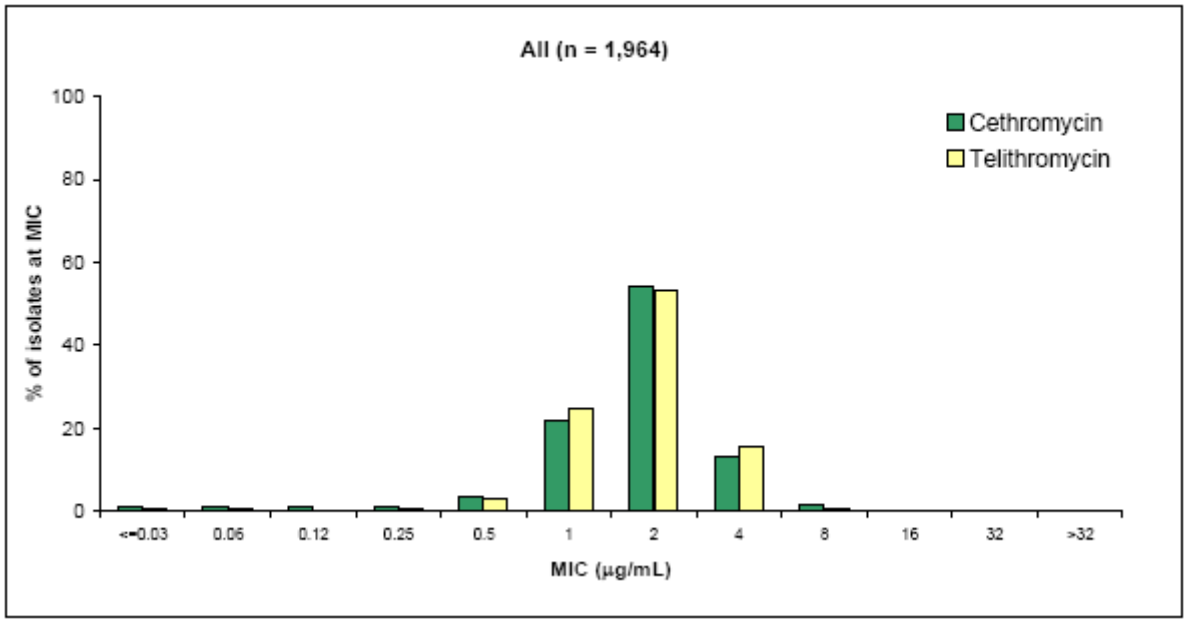
Table 6: Comparative *In Vitro* Activity of Antibiotics Against *H. influenzae*

Phenotype (N)	Cethromycin		Telithromycin		Clarithromycin		Azithromycin		Erythromycin	
	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}
β-lactamase negative (5,864)	≤0.002 – ≥8	4	≤0.002 – ≥32	2	≤0.06 – ≥128	16	≤0.06 – ≥128	2	≤0.12 – >256	16
BLNAR (53)	0.03 – 4.0	4	0.12 – 4	4	0.25 – 32	16	1.0 – 4.0	4	4.0 – 16	16
β-lactamase positive (1,702)	≤0.002 – ≥8	4	≤0.002 – ≥32	2	≤0.06 – ≥128	16	≤0.06 – ≥128	2	0.25 – 64	16

MIC unit: μg/mL; BLNAR: β-lactamase-negative, ampicillin-resistant

The potent *in vitro* activity of cethromycin was recently confirmed against approximately 2,000 clinical *H. influenzae* isolates collected in the USA and Europe from 2004 to 2007. The MIC distribution for cethromycin and telithromycin is shown in Figure 2.

Figure 2: MIC Distribution for Cethromycin and Telithromycin for *H. influenzae*: USA and Europe



4.3.3 *Moraxella catarrhalis*

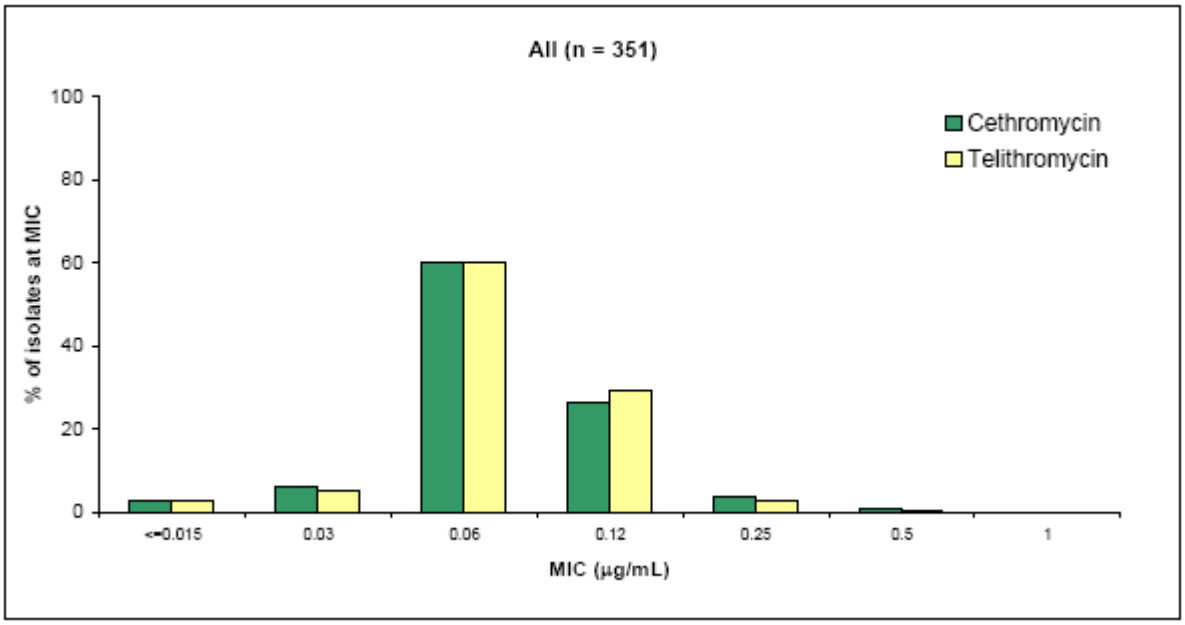
Over 90% of all *M. catarrhalis* isolates, a common respiratory tract pathogen, produce β-lactamases that render them resistant to antibacterial agents such as amoxicillin. Cethromycin displayed excellent *in vitro* activity against *M. catarrhalis* with MIC_{90} values of 0.12 μg/mL, regardless of the β-lactamase status of the isolate (Table 7). This activity is similar to azithromycin and telithromycin but 2- to 4-fold more potent than erythromycin and clarithromycin.

Table 7: Comparative *In Vitro* Activity of Antibiotics Against *M. catarrhalis*

Phenotype (N)	Cethromycin		Telithromycin		Clarithromycin		Azithromycin		Erythromycin	
	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}
β-lactamase negative (50)	0.03 – 0.12	0.12	0.03 – 0.25	0.12	0.12 – 0.5	0.5	0.03 – 0.06	0.06	0.12 – 0.5	0.25
β-lactamase positive (428)	0.015 – 0.25	0.12	0.015 – 0.25	0.12	0.12 – 0.5	0.25	0.03 – 0.06	0.06	0.12 – 0.5	0.25

The potent *in vitro* activity of cethromycin was recently confirmed against approximately 400 clinical *M. catarrhalis* isolates collected in the USA and Europe from 2004 to 2007. The MIC distribution for cethromycin and telithromycin is shown in Figure 3.

Figure 3: MIC Distribution for Cethromycin and Telithromycin for *M. catarrhalis*: USA and Europe



4.3.4 *Staphylococcus aureus*

Although more often associated with skin and soft tissue infections, *S. aureus* is also an important causative agent of CAP. Of increasing concern are reports of MRSA infections in the outpatient setting.

Erythromycin resistance is invariably present in MRSA. It was reported that there was 8.2% resistance to erythromycin among methicillin-susceptible *S. aureus* (MSSA) isolates and 87.9% erythromycin resistance among MRSA isolates.[36]

Cethromycin exhibited excellent *in vitro* activities against *S. aureus* isolates that are susceptible to methicillin, resistant to methicillin but susceptible to macrolides, or resistant to macrolides due to the inducible MLS_B phenotype (Table 8).[37] Against MSSA, cethromycin activity is comparable to the fluoroquinolones and telithromycin but at least 256-fold more active than the macrolides. MRSA isolates with a MLS_B phenotype, resulting in constitutive production of *erm*A or *erm*C methylase, are resistant to cethromycin as well as all other macrolides and ketolides.[23,38]

Table 8: Comparative *In Vitro* Activity of Antibiotics Against *S. aureus*

Phenotype (N)	Cethromycin		Telithromycin		Clarithromycin		Azithromycin		Erythromycin	
	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}
MSSA (180)	≤0.01 – 0.06	0.06	0.03 – 0.25	0.06	≤0.01 – 16	16	0.25 – 64	32	0.12 – 64	64
MRSA/Ery-S (86)	≤0.031	≤0.031	ND	ND	≤0.031 – 0.125	0.063	ND	ND	0.125 – 0.5	0.125
MRSA/MLS_B inducible (53)	≤0.031	≤0.031	ND	ND	1 – >128	>128	ND	ND	2 – >128	>128
MRSA/MLS_B constitutive (40)	>128	>128	>128	>128	>128	>128	ND	ND	>128	>128
*erm*A/inducible (11)	0.03 – 0.25	0.25	0.03 – 0.5	0.5	2 – >128	>128	8 – >128	>128	4 – >128	>128
*erm*A or *erm*C/ constitutive (60)	≤0.008 – >32	>32	0.06 – >32	>32	------	------	------	------	16 – >32	>32

MIC unit: µg/mL; ND = not determined

USA300, a clone of CA-MRSA, has been implicated in several outbreaks in the USA and is resistant to most currently marketed antimicrobial agents. Against 170 community-acquired MRSA USA300 isolates tested, cethromycin was very effective, with an MIC range of 0.002 – 0.125 μg/mL. In contrast, 169 (99.4 %) of these isolates displayed decreased susceptibility to at least one macrolide (Table 9).

Table 9: MICs of Cethromycin and Comparative Agents Against 170 Community-Acquired MRSA USA300 Isolates

	Antimicrobial Agent				
MICs (μg/mL)	**Cethromycin**	**Azithromycin**	**Clarithromycin**	**Clindamycin**	**Erythromycin**
MIC range	≤0.002 - 0.125	1 - >256	≤0.12 - >8	0.06 - >256	≤0.12 - >256
MIC_{50}	≤0.002	>256	>8	0.12	128
MIC_{90}	≤0.002	>256	>8	0.25	256
no. susceptible [a]	NA [b]	10	15	164 [c]	10
no. intermediate [a]	NA [b]	1	1	0	6
no. resistant [a]	NA [b]	159	154	6 [d]	154

[a] Based on MIC breakpoints recommended by CLSI: azithromycin: ≤ 2 mg/L, susceptible and ≥ 8 mg/L, resistant; clarithromycin: ≤ 2 mg/L, susceptible and ≥ 8 mg/L, resistant; clindamycin: ≤ 0.5 mg/L, susceptible and ≥ 4 mg/L, resistant; erythromycin: ≤ 0.5 mg/L, susceptible and ≥ 8 mg/L, resistant.

[b] NA, not applicable; approved breakpoints are not established yet for cethromycin.

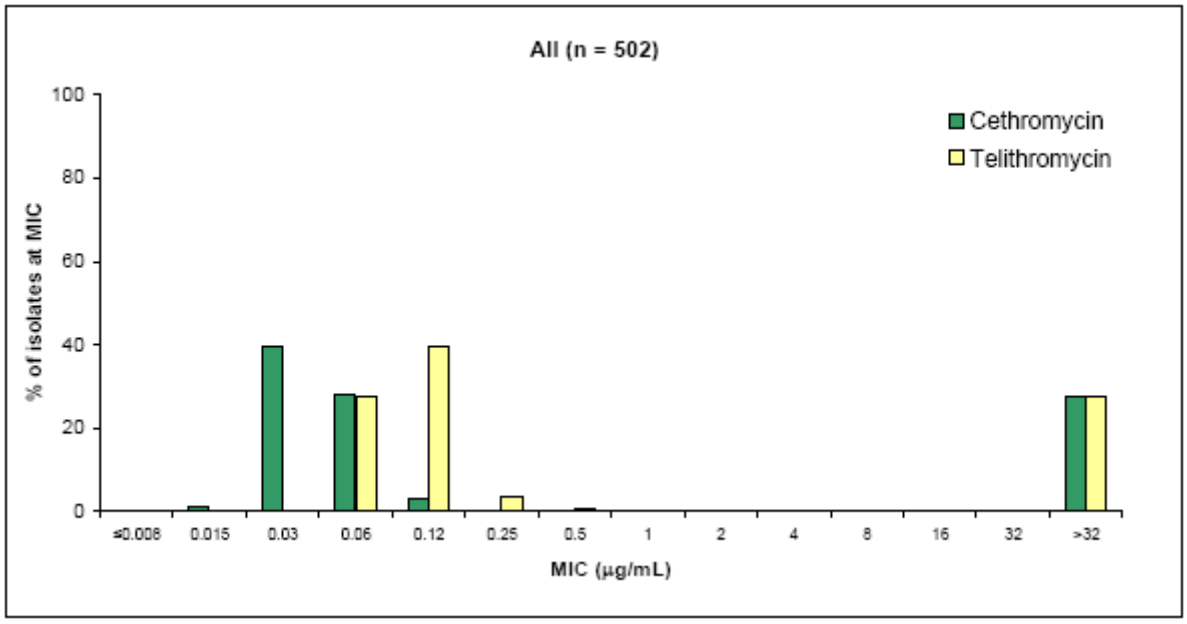
[c] All 164 isolates susceptible to clindamycin remained susceptible in the presence of erythromycin.

[d] Two of the 6 resistant strains displayed inducible resistance while 4 resistant isolates demonstrated constitutive resistance.

S. aureus produces a variety of virulence factors that contribute to the pathogenicity of some clinical isolates. One type of virulence factor is represented by the Panton-Valentine leukocidin (PVL) genes which encode toxins that damage the cell membrane of host defense cells and erythrocytes.[39] In 48 *S. aureus* clinical isolates collected from the cethromycin pivotal CAP program, PVL genes *lukF*-PV and *lukS*-PV were identified in 2 isolates, both susceptible to cethromycin with MIC values of 0.06 and 0.12 μg/mL, respectively.

The potent *in vitro* activity of cethromycin was recently confirmed against approximately 500 clinical *S. aureus* isolates collected in the USA and Europe from 2004 to 2007. The MIC distribution for cethromycin and telithromycin is shown in Figure 4.

Figure 4: MIC Distribution for Cethromycin and Telithromycin for *S. aureus*: USA and Europe



4.3.5 Atypical and Intracellular Pathogens

M. pneumoniae, *C. pneumoniae,* and *L. pneumophila* infections are common causes of atypical pneumonia. Both *C. pneumoniae* and *L. pneumophila* are intracellular pathogens; *L. pneumophila* produces β-lactamase and can survive and multiply within alveolar macrophages. These atypical pathogens are refractory to therapy with the β-lactam class of antimicrobials. Cethromycin was an extremely potent inhibitor of *C. pneumoniae* (MIC_{90} = 0.015 μg/mL), *M. pneumoniae* ($MIC_{90} \leq 0.001$ μg/mL), and *L. pneumophila* ($MIC_{90} \leq 0.06$ μg/mL or less). Among the macrolides and ketolides tested, cethromycin was the most potent (Table 10).[40,41,42]

Table 10: Comparative *In Vitro* Activity of Antibiotics Against Atypical and Intracellular Pathogens

Microorganism (N)	Cethromycin		Telithromycin		Clarithromycin		Azithromycin		Erythromycin	
	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}
C. pneumoniae (20)	0.008 – 0.015	0.015	0.015 – 0.25	0.06	0.015 – 0.125	0.06	0.015 – 0.125	0.125	0.015 – 0.06	0.06
M. pneumoniae (203)	≤0.001 – 0.016	≤0.001	≤0.015	≤0.015	≤0.001 – 0.04	≤0.001	≤0.001	≤0.001	≤0.001 – 0.016	≤0.004
L. pneumophila (68)	0.015 – 0.06	0.06	0.015 – 0.25	0.25	0.03 – 0.06	0.06	<0.06 – 2.0	2	0.125 – 1.0	1

4.3.6 Summary of *In Vitro* Activity

Cethromycin:

- demonstrates potent *in vitro* activity against the CAP target pathogens *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila.*
- is highly active against *S. pneumoniae* including penicillin- and macrolide-resistant strains (*erm*B, *mef*[A,E]), and against strains resistant to tetracycline, trimethoprim-sulfamethoxazole, and ciprofloxacin.
- is effective against *H. influenzae*, regardless of whether the isolates were β-lactamase-negative or -positive, or β-lactamase-negative but ampicillin-resistant.
- is extremely potent against *M. catarrhalis* (β-lactamase-negative or -positive).
- is extremely potent against the atypical pathogens.
- surveillance studies conducted with clinical isolates provide a comprehensive description and corroborate the potent antimicrobial activity of cethromycin against key target CAP pathogens.

Thus, against the key organisms responsible for CAP, cethromycin demonstrated excellent *in vitro* activity in preclinical studies as well as in large surveillance studies of clinical isolates.

4.4. Bactericidal Activity

Cethromycin demonstrated superior killing properties relative to the macrolides and azalides. The bactericidal activity of cethromycin has been evaluated against multiple strains of *S. pneumoniae* (including strains containing *erm*, *ermB*, *mef*, and *mefE*), *H. influenzae*, *M. catarrhalis*, *C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*.. The majority of the assays were conducted at concentrations of 2- and 8-fold MIC. In general, killing at 8-fold MIC was greater than that achieved at 2-fold MIC. At 8-fold MIC, cethromycin was bactericidal against many of the test isolates, including both macrolide-susceptible and macrolide-resistant strains, with some modest variability between similar studies. Cethromycin killing appears reduced for some strains of pneumococci that harbor the *ermB* gene, although the compound is bactericidal for others. Bactericidal activity was observed for streptococci containing *mef*, *mefA*, and *mefE* genes.

In both neutropenic and immunocompetent murine pneumococcal pneumonia models, both AUC_{free}/MIC and $C_{max\ free}$/MIC ratios appeared to best explain the relationship between drug exposure and cethromycin efficacy.[43] In the presence of neutrophils, lower drug exposure was required to produce the same degree of bacterial killing when compared with a neutropenic host. The AUC_{free}/MIC ratio required to achieve a bacteriostatic effect was 2.5-times lower and the ratio needed to achieve a bactericidal effect was 4-times lower in the immunocompetent host.[44]

4.5. Postantibiotic Effect

The suppression of bacterial growth that persists after short exposure of organisms to antimicrobial agents is known as the postantibiotic effect (PAE). A significant body of evidence was developed that characterizes cethromycin as an antibacterial agent with a prolonged *in vitro* PAE for its key target organisms including *S. pneumoniae* (>1.7 hours) and *H. influenzae* (>4.9 hours). This effect is attributed to the molecule's tight binding to bacterial ribosomes that, in turn, delays the resumption of normal cell growth and division even after the drug removal. The demonstration that cethromycin produces serum and tissue levels in excess of the MICs of susceptible organisms indicates that the PAE of cethromycin (as measured *in vitro*) should be realized in clinical practice. Therefore, the prolonged PAE of cethromycin should contribute to the overall antibacterial activity of the compound.

4.6. *In Vitro* Antimicrobial Interaction

The *in vitro* activity of cethromycin was assessed in combination with numerous other antibacterial agents against individual representative strains of Gram-positive and Gram-negative bacteria. The results demonstrated additive interactions with most antibacterial agents tested and a synergistic interaction with doxycycline. No evidence of antagonism was observed for any of the drug combinations with the test strains. This is important since there are clinical circumstances where the use of two antibacterial agents in a given patient may occur.

4.7. Animal Models of Infection

4.7.1 Systemic Infections

Orally administered cethromycin was found to be effective in protecting mice against lethal systemic infection.[45] The efficacy of cethromycin administered orally was compared to that of clarithromycin and azithromycin and efficacy was quantified as the mean effective (curative) dose 50% (ED_{50}).

Cethromycin was more effective than azithromycin against *S. aureus* and *S. pneumoniae* systemic infections. The activities of cethromycin, clarithromycin, and telithromycin evaluated by the mouse protection model are shown in Table 11.

Table 11: *In Vivo* Efficacy of Cethromycin for Treatment of Systemic Infections in Mice

	Oral ED_{50} (mg/kg)			
Test Drug	***S. aureus*** 10649	***S. pneumoniae*** 6303	***S. pyogenes*** C203	***L. monocytogenes*** 2526
Cethromycin	9.5	10.0	1.9	100.1
Clarithromycin	30.2	37.3	3.7	>200
Telithromycin	12.8	34.0	–	–

In another study, cethromycin was more effective than clarithromycin for treating systemic infection caused by macrolide-susceptible and penicillin-resistant *S. pneumoniae*. Penicillin failed against the resistant isolate, but was effective against the susceptible strain (Table 12).

Table 12: MIC and ED_{50} Values for Cethromycin vs. Macrolide-Sensitive (MLS-S), Penicillin-Susceptible and -Resistant (Pen S, Pen R) *S. pneumoniae* Systemic Infections

	***S. pneumoniae* 6303 MLS-S, Pen-S**		***S. pneumoniae* 6502 MLS-S, Pen-R**	
Test Drug	**MIC[a]**	**ED_{50}**	**MIC[a]**	**ED_{50}**
Cethromycin [b]	0.001	4.6	0.001	12.4
Penicillin[c]	0.015	<12.5	4	167.4
Clarithromycin [b]	0.008	8.3	0.015	16.5

a MIC values in µg/mL
b Administered orally. ED_{50} values in mg/kg
c Administered subcutaneously. ED_{50} values in units/kg

Cethromycin was more effective than clarithromycin for treating systemic infection caused by macrolide-resistant *S. pneumoniae* (Table 13). The isolates of *S. pneumoniae* tested included MLS-resistant strains, which were penicillin-susceptible, intermediate and resistant. Penicillin and clarithromycin failed against resistant isolates, but were effective against the susceptible strain. Cethromycin demonstrated moderate (ED_{50} = 50 mg/kg) to good (ED_{50} = 10 mg/kg)

efficacy against macrolide-resistant strains, while clarithromycin therapy failed (ED_{50} = 100 to >200 mg/kg). Activity data are summarized in Table 13. [45]

Table 13: Efficacy of Cethromycin Against Macrolide-Resistant *S. pneumoniae* (Pen S, I/R Strains)

Test Drug	*S. pneumoniae* 6396 Pen-S/*erm*B		*S. pneumoniae* 5669 Pen-I/*erm*B		*S. pneumoniae* 5979 Pen-R/*erm*B	
	MIC[a]	ED_{50}	MIC[a]	ED_{50}	MIC[a]	ED_{50}
Cethromycin [b]	0.015	50.1	0.002	14.7	0.002	10.3
Penicillin[c]	0.06	22.2	1	24.1	4	>800
Clarithromycin [b]	>128	>200	>128	123.8	>128	>200

a MIC values in µg/mL
b Administered orally. ED_{50} values in mg/kg
c Administered subcutaneously. ED_{50} values in units/kg

4.7.2 Pulmonary Infections

Cethromycin was markedly superior to azithromycin against rat pulmonary infections caused by *S. pneumoniae* isolates both susceptible and resistant to penicillin and macrolides.[46] Cethromycin demonstrated good efficacy against all strains of *S. pneumoniae* tested including MLS and efflux macrolide-resistant strains, and penicillin-susceptible, intermediate, and resistant strains. Efficacy against pulmonary infections was determined by monitoring bacterial reductions (2 $\log_{10}$ CFU) in the lung tissue of study rats (Table 14). These studies in rats demonstrated successful use of cethromycin against pulmonary infections caused by macrolide-resistant *S. pneumoniae*.

Table 14: Efficacy of Cethromycin Against Macrolide-Susceptible and -Resistant *S. pneumoniae* Pulmonary Infection

Test Drug	*S. pneumoniae* 6303 Pen-S/MLS-S		*S. pneumoniae* 5649 Pen-I/*mef*E		*S. pneumoniae* 6396 Pen-S/*erm*B	
	MIC[a]	ED_{50}[b]	MIC[a]	ED_{50}[b]	MIC[a]	ED_{50}[b]
Cethromycin	0.001	<0.6	0.06	11.8	0.015	1.6
Clarithromycin	0.008	3.7	4.0	41.9	>128	>100
Azithromycin	0.03	3.7	8.0	24.9	>128	>100
Telithromycin	0.015	2.3	0.25	25.8	0.125	26.7

a MIC values in µg/mL
b ED_{50} values in mg/kg

Additionally in rats, QD dosing was found to be as effective as BID dosing (when the same total daily quantity of drug was administered) for the treatment of macrolide-resistant *S. pneumoniae* pulmonary infections.[46] This observation was also noted against *H. influenzae* infection (data not shown).[47]

Cethromycin was evaluated in both rat and mouse infection models for its ability to treat *H. influenzae* pulmonary infection. Oral therapy with cethromycin was similar to azithromycin and was an improvement over clarithromycin in the treatment of *H. influenzae* pulmonary infection in rat and mouse disease models (Table 15).[46,47]

Table 15: Efficacy of Cethromycin Against *H. influenzae* Pulmonary Infection in the Rat

Test Drug	*H. influenzae* 1435		*H. influenzae* 3643	
	MIC[a]	ED_{50}[b]	MIC[a]	ED_{50}[b]
Cethromycin	0.5	19.8	2	29.0
Clarithromycin	2	109.8	4	67.8
Azithromycin	1	55.4	1	44.2
Telithromycin	0.5	64.6	1	52.9

a MIC values in µg/mL
b ED_{50} values in mg/kg

4.8. Metabolites

The major metabolite of cethromycin seen in all animal species and human is the N-desmethyl derivative (M1). The *in vitro* activity of M1 was shown be 2- to 4-fold less active than cethromycin against representative Gram-positive bacteria, and 4- to 8-fold less active than cethromycin against representative Gram-negative bacteria.[48]

5. NONCLINICAL PHARMACOLOGY, TOXICOLOGY AND PHARMACOKINETICS

5.1. Nonclinical Pharmacology and Toxicology

Nonclinical pharmacology studies evaluated the effect of cethromycin on the central nervous system, pulmonary system, cardiovascular system, and gastrointestinal system.

The toxicity profile of cethromycin has been investigated in rats and monkeys after repeated oral dosing of two weeks, one month, and three months duration. Most of these studies included measures of toxicokinetics and reversibility of the changes was assessed after 1- and 3-month dosing. In addition, reproductive toxicity studies were carried out in rats and rabbits. Cethromycin was also tested for genotoxicity in a standard battery of tests.

5.1.1 Central Nervous System

Cethromycin was evaluated for potential central nervous system effects in tests of locomotor activity, motor coordination, hypnotic potentiation, proconvulsant/anticonvulsant activity, and nociception in mice and rats. The mild findings in mice and rats were not considered to be toxicologically significant.

5.1.2 Pulmonary System

The pulmonary safety profile of orally administered cethromycin was assessed in conscious rats. The data demonstrated that cethromycin did not substantially affect pulmonary function at doses up to 180 mg/kg.

5.1.3 Cardiovascular System

Cethromycin was tested *in vitro* for its ability to block hERG. Cethromycin was shown to block 50% of the hERG tail current at 22.1 μg/mL or 732-fold above the mean free cethromycin human plasma concentration at the therapeutic dose of 300 mg QD, with minimal blockage at 5.0 μg/mL or 166-fold above, and no blockage at 0.5 μg/mL or 17-fold above the estimated free plasma concentration of cethromycin.

Cethromycin and M1 were evaluated *in vitro* for their ability to alter the action potential duration (APD) in Purkinje fibers isolated from adult beagle dogs. Cethromycin caused dose-dependent prolongation of the canine APD at concentrations of ≥5 μg/mL, a 166-fold margin; the margin at the no observed effect level (NOEL) concentration (0.5 μg/mL) was 17-fold. M1 also caused prolongation of the canine APD but only at the highest concentration tested, 12.5 μg/mL, 39-fold above the mean M1 plasma level seen in humans following a therapeutic dose of cethromycin (300 mg QD).

In both anesthetized and conscious dogs administered step-up 30-min intravenous infusions of cethromycin, slightly increased blood pressure, decreased heart rate, and QT_C interval prolongation were observed. Hemodynamic changes observed were mild in nature and are thought to be related to an increased peripheral vascular resistance which reflexively decreased heart rate and cardiac output. In the conscious dog study, mild increases in blood pressure

occurred at free cethromycin plasma levels of 0.69 µg/mL and QT/QT_C prolongation occurred at 2.12 µg/mL; 23-fold and 70-fold margins, respectively. No increases in blood pressure and QT/QT_C intervals were seen in conscious dogs at 7-fold (0.22 µg/mL free) and 34-fold (1.02 µg/mL free) margins, respectively.

Toxicology studies with non-human primates revealed no significant prolongation of the QT_C interval despite long-term exposure to supratherapeutic plasma levels of the compound. Results demonstrated that cethromycin did not prolong the QT_C interval at any dosing regimen.

5.1.4 Gastrointestinal System

5.1.4.1. Effects on Gastrointestinal Motility

Potential interactions of cethromycin with the gastrointestinal tract were investigated using both *in vitro* (guinea pig ileum, rabbit duodenum) and *in vivo* (gastric emptying/propulsion in mice) models. No direct effect of cethromycin was observed on contracting smooth muscle associated with the guinea pig ileum; however, contraction was seen in rabbit duodenum with half-maximum contraction occurring at 31.6 µM (24.2 µg/mL). Cethromycin was also shown to accelerate gastric emptying and propulsion time in mice receiving a charcoal meal. During toxicity studies in dogs and monkeys, cethromycin was reported to induce emesis and loose stools/diarrhea. These results indicate a potential for side effects related to gastrointestinal effects at high doses. [49]

5.1.4.2. Effects on the Liver

There were no liver effects seen in the 2-week toxicology studies in rats at doses up to 500 mg/kg/day and in monkeys at doses up to 200 mg/kg/day. Mild, reversible hepatic effects (i.e., increased liver weight, microscopic findings indicative of phospholipidosis, and/or mildly increased serum concentration of liver-specific enzymes) were observed in the one month studies in rats and monkeys at doses of 60 and 70 mg/kg/day respectively. In the 3-month toxicology studies in rats at ≥20 mg/kg/day, a low incidence of minimal portal tract scarring was observed, in addition to evidence of phospholipidosis at 20 and 60 mg/kg/day. In monkeys at three months there were no effects at 25 mg/kg/day (Table 16).

Table 16: Treatment-Related NOAEL for Liver Findings

Species	NOAEL for Treatment-Related Liver Finding[a]		
	2-Week[b]	1-Month	3-Month
Rat	> 500 mg/kg (>59x)	60 mg/kg (male: 16x[c]; female: 24x)	20 mg/kg (male: 8x[c]; female: 11x)
Monkey	> 200 mg/kg (>14x)	70 mg/kg (36x)	>25 mg/kg (5x)

a Number in parentheses is the fold-exposure compared to the mean steady state free human plasma concentration at 300 mg QD.
b No liver effects were seen in the 2-week study in either rat or monkey.
c Lower exposure was observed in male rats than in females, consistent with greater CYP3A activity in the males.

5.1.4.3. Phospholipidosis-associated Changes

Phospholipidosis, characterized by ultrastructural appearance of membranous lamellar inclusions, particularly lysosomal in origin, occurred in the liver and to a lesser extent in the kidney. These were shown to be mostly reversible. Light microscopic findings indicative of phospholipidosis included increases in foamy alveolar macrophages, pigmented Kupffer cells, and hepatocytes. At 13 weeks, minimal effects on biliary epithelium possibly associated with phospholipidosis were observed in rats at all doses. Classical ultrastructural changes, e.g., lysosomes with or without lamellae, were observed in kidney distal tubule epithelial cells in rats. Classical phospholipidosis-related accumulation of alveolar foamy macrophages was seen in rats at ≥60 mg/kg/day; these changes were considered adverse at high doses. The NOAEL for target organ changes considered related to phospholipidosis is 20-fold (4 weeks) and 9-fold (13 weeks) in rats and 36-fold (4 weeks) and 5-fold (13 weeks) in monkeys.

Phosholipidosis is normally considered adaptive and has been commonly observed in studies with macrolides and other ketolide agents such as erythromycin, azithromycin, and telithromycin.

5.1.5 Reproductive Toxicity

Reproductive toxicity studies were carried out in the rat and rabbit to assess the effects of cethromycin on fertility, embryonic and fetal development, and pre- and post-natal development.

There was no evidence of cethromycin-related teratogenicity in rats or rabbits at maternotoxic doses. Fertility was not affected in female rats up to 180 mg/kg/day (140-fold margin). F1 rat pups exhibited decreased body weights, delayed eye opening, and pinna detachment at maternotoxic doses. The NOAEL in this study for delayed development findings is 25 mg/kg/day or a 7-fold margin.

In the rabbit embryofetal study there was no evidence of any effect on fetal survival or development despite maternal toxicity (e.g., mortality, rales, oral discharge, and dark/red urine at ≥30 mg/kg/day and decreased body weight and mortality at 100 mg/kg). The NOAEL for developmental effects in rabbits is 100 mg/kg/day or a 16-fold margin based on total plasma levels of cethromycin area under the concentration curve (AUC) generated at the therapeutic dose.

Testicular atrophy/degeneration and spermatid degeneration were reported in rats. These findings occurred in studies of 4-week duration or longer, and were seen at exposure margins of 37-fold (4 weeks) and 31-fold (13 weeks), with NOAELs at 59-fold (2 weeks), 16-fold (4 weeks), and 8-fold (13 weeks). Testicular changes were not seen in monkeys at similar exposures for up to 13 weeks in duration. Because of the exposure margins in shorter duration studies, which are more relevant for the human dosing duration of 7 days, and since this finding was not observed in monkeys at high doses over a 13-week period, these findings are not considered to be of concern as far as a risk to males at the dose and duration proposed for cethromycin use.

Male rats showed a decrease in the ability to impregnate untreated females attributable to testicular atrophy/degeneration. Male rats also showed a decrease in fertility at highly exaggerated doses; this was considered to be secondary to the atrophy of seminal vesicles leading to inadequate copulatory plug formation, a mechanism irrelevant to humans. The

NOAEL for male reproductive effects in rats is 20 mg/kg/day for 9 weeks of treatment, a 4-fold exposure margin.

5.1.6 Genotoxicity

Cethromycin was not genotoxic in either *in vitro* (cytogenetics study in human lymphocytes, Ames test, or mouse lymphoma mutagenesis assay) or i*n vivo* (mouse micronucleus) studies.

5.2. Pharmacokinetics

The pharmacokinetics of cethromycin was studied in rats, dogs, and monkeys after single and repeated doses, with greater emphasis on the primary toxicology species, i.e., rats and monkeys, after oral administration and on the cardiovascular safety pharmacology species, i.e., dogs, after intravenous administration.

Absorption of cethromycin varied among the species tested, with peak plasma concentrations generally occurring in the 1.5-6 h range and with oral bioavailability in the range of 36 to 60%. Half-lives of cethromycin after oral administration were between 2.3 to 6.0 hours. Following oral administration of cethromycin to rats and monkeys, plasma exposure for both cethromycin and M1 generally increased in a dose proportional manner up to the maximum dose evaluated (500 mg/kg) in rats and at doses up to 100 mg/kg in monkeys.

No evidence of accumulation of cethromycin was noted in the dog or monkey; however, accumulation of M1 was noted in monkeys at the high dose. Accumulation of cethromycin was noted at ≥60 mg/kg/day and M1 at ≥20 mg/kg/day in the repeat-dose studies in rats. Bioavailability generally increased with repeated dosing in rats. In pregnant rats, exposure to cethromycin was substantially higher after repeated dosing than in nonpregnant rats; AUCs in pregnant rats were about 4-fold those of nonpregnant rats from 60-180 mg/kg/day. Plasma exposure of both cethromycin and M1 were slightly lower in juvenile rats versus adults from 60-180 mg/kg/day.

There were no significant sex differences in the pharmacokinetics of cethromycin or M1 in dogs and monkeys. Female rats, however, showed approximately 1.5 – 3 times higher plasma levels of both the parent and metabolite versus male rats after multiple oral doses, which is consistent with greater CYP3A activity in the males.

The cethromycin volume of distribution ranged from approximately 2 - 9 L/kg, values greater than the volume of total body water, indicating good distribution of cethromycin to tissues. [^{14}C]-cethromycin was shown to be widely distributed to tissue, with levels similar to or greater than plasma in most tissues over 24 hours. Relative to plasma, lower levels were consistently seen in brain and eyes. The highest levels were associated with organs of absorption (gastrointestinal tract), metabolism (liver), and excretion (kidney). Other tissues with particularly high concentrations relative to plasma included adrenals, bone marrow, lung, thyroid, and spleen.

All metabolites identified in humans were also identified in rats and monkeys, the species used for repeated dose oral toxicity studies. The results of the non-clinical program thus support the safety of the M1 metabolite in humans at the intended dose and duration proposed.

Fecal elimination of radioactivity predominated in rats, dogs, and monkeys after both intravenous and oral administration. Urinary excretion of cethromycin and its metabolites was low across all species.

Over the concentration range of 0.1 – 10 μg/mL, cethromycin binding to serum proteins was approximately 95.0% in human, 92.6% in mouse, 89.7% in rat, 86.1% in dog, and 83.8% in monkey. No sex differences in binding were observed in any species. Cethromycin was not extensively bound to human serum albumin, but was bound to α_1-acid glycoprotein.

6. CLINICAL PHARMACOKINETICS

6.1. Absorption, Distribution, Metabolism, and Elimination

6.1.1 Absorption and Bioavailability

Absorption following administration of a single oral dose to humans was fairly rapid at 1-3.5 hours and the extent of absorption was estimated to be 55-60% of the dose based on excretion of absorbed radioactivity. Food did not have an effect on the pharmacokinetic profile of cethromycin.

6.1.2 Distribution

Cethromycin was about 87-95% protein bound at clinically relevant concentrations, with binding to α1-acid glycoprotein being of higher affinity than to albumin, and accounting for most of the binding. There was no significant difference in plasma protein binding between healthy subjects and subjects with mild to moderate hepatic impairment or subjects with severe renal impairment.

Cethromycin does not have an obvious distribution phase as part of the concentration-time profile following oral administration, indicating that the distribution processes are occurring simultaneously with absorption. With 300 mg QD dosing, cethromycin has an apparent volume of distribution of 588 L after a single dose and 652 L at steady-state. These apparent volumes are 7- to 9-times body weight, suggesting that much of the drug is rapidly distributed into tissue spaces from the plasma.

Cethromycin is distributed equally between plasma and blood cells. Intracellular exposures to cethromycin in lung tissues are over 100-fold greater than in plasma (Table 17).

Table 17: Concentrations in Plasma, Epithelial Lining Fluid and Alveolar Macrophages After Multiple Oral Doses of 300 mg QD for 5 days

Time (hours)	Cethromycin (μg/mL)		
	Plasma	Epithelial Lining Fluid	Alveolar Macrophages
2	0.25	2.5 (10)	22.6 (90)
4	0.38	2.7 (7)	48.5 (128)
8	0.09	0.9 (10)	22.6 (251)
12	0.1	0.8 (8)	33.6 (336)
24	0.01	0.1 (10)	6.7 (670)
48	0	0	3.7 (∞)

Numbers in parentheses refer to fold increase over plasma concentration.

6.1.3 Metabolism

The predominant molecular species in plasma over the entire time span was the parent molecule, suggesting that there is little first-pass effect. Cethromycin undergoes biotransformation via CYP3A hydroxylation and N-desmethylation, primarily to M1. In addition, up to six other

minor metabolites have been detected in humans. Plasma exposures to cethromycin are approximately 4-fold greater than to M1.

6.1.4 Elimination

Cethromycin has a dose-independent terminal half-life of 5-8 hours. Cethromycin clearance was dose-dependent and consistent with saturable elimination; a 37% higher apparent clearance was observed at half the dose, and a 25% lower apparent clearance was observed at twice the dose. At steady-state, the apparent oral clearance following administration of 300 mg QD in healthy volunteers was approximately 72 L/hr.

Following oral administration of 150 mg of radiolabeled cethromycin, 87% of the dose was recovered in feces and 7% was recovered in urine, resulting in a mean recovery of 94%. In feces, cethromycin and M1 each accounted for approximately one-third of the total radioactivity, and the remainder was a mixture of metabolites, with none accounting for more than 6% of the total radioactivity. In urine, cethromycin accounted for about 6% of the total radioactivity, and the remainder was attributed to M1.

6.2. Pharmacokinetics

6.2.1 Basic Pharmacokinetics

Following administration of 300 mg cethromycin, peak plasma concentrations were observed at a median of 2 to 3 hours for both cethromycin and M1 (N-desmethylcethromycin) (Figure 5). AUC values were mildly increased at steady-state relative to a single dose for both cethromycin and M1 (14% and 19%, respectively, with the 300 mg dose). The half-life for the parent was approximately 5 to 6 hours, and that for the metabolite was approximately 7 to 8 hours. Cethromycin pharmacokinetic parameters are presented in Table 18.

Figure 5: Mean Plasma Concentration Profiles of Cethromycin and N-Desmethylcethromycin Following Administration of Cethromycin 300 mg QD

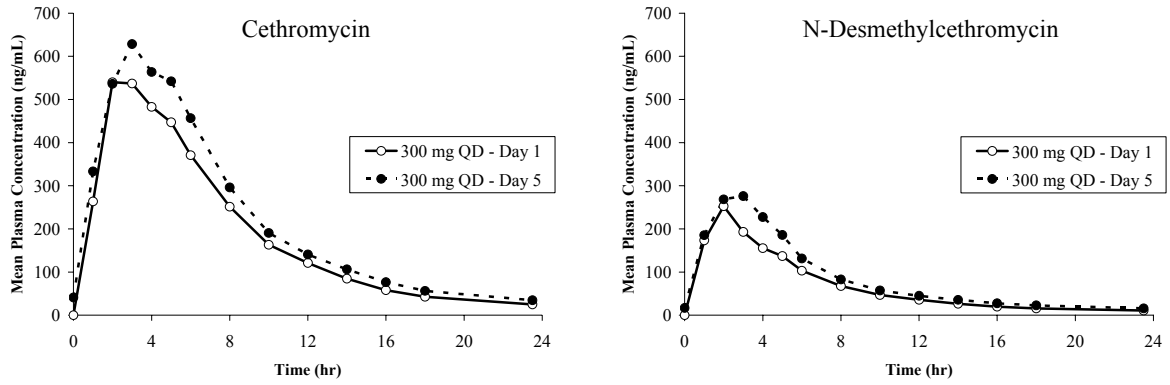


Table 18: Cethromycin Pharmacokinetic Parameters

	Cethromycin 300 mg QD n = 59	
	Day 1 Mean (% CV)	Day 5 Mean (% CV)
Cethromycin		
AUC (hr·ng/mL)[a]	4605 (50)	5237 (52)
C_{max} (ng/mL)	592 (45)	686 (51)
T_{max} (hr)[b]	2.0 (1.0, 6.0)	3.0 (1.0, 6.0)
$T_{1/2}$ (hr)	5.03 (27)	6.12 (31)
CL/F (L/hr)[c]	82.1 (50)	71.9 (48)
Vz/F (L)[c]	588 (56)	652 (62)
M1 (N-Desmethylcethromycin)		
AUC (hr·ng/mL)[a]	1660 (44)	1974 (43)
C_{max} (ng/mL)	280 (44)	324 (41)
T_{max} (hr)[b]	2.0 (1.0, 5.0)	2.0 (1.0, 5.0)
$T_{1/2}$ (hr)	7.20 (29)	8.38 (33)

CV = coefficient of variation
a AUC(0–∞) for Day 1; AUC(0–24) for Day 5.
b Median (minimum, maximum) for Tmax.
c Calculated separately.

6.2.2 Body Weight, Age, Gender, and Race

Examination of the trends in the clinical studies and/or meta-analyses indicated that race and gender did not have an effect on the pharmacokinetic profile of cethromycin, and that increased body weight only weakly correlated with decreased exposures to cethromycin. Therefore, no dose adjustments based on body weight, gender, or race alone will be recommended.

Increased age had a modest, but weak, correlation with increased cethromycin exposures in the Phase I meta-analyses. However, examination of cethromycin concentrations and renal function in older patients in the Phase III meta-analyses revealed that older patients tended to have mild or moderate renal impairment, and their increased cethromycin concentrations reflected the impact of the decreased renal function. Given the high variability in cethromycin plasma concentrations, and the lack of an increase in adverse events in older subjects with elevated cethromycin exposures in plasma, no dose adjustments based on age will be recommended.

6.2.3 Renal and Hepatic Impairment

There were no clinically meaningful changes in cethromycin plasma exposures observed in subjects with mild or moderate hepatic impairment relative to matched-control subjects following administration of the 300 mg QD dosing regimen (changes of ≤27% in both subject groups). Similarly, in the Phase I meta-analyses, subjects with impaired hepatic function had slightly lower peak exposures, but similar total exposures, compared with subjects with normal hepatic function. Therefore, no dosage adjustment for cethromycin is needed in patients with

mild or moderate hepatic impairment. Since no studies have yet been conducted in adult patients with severe chronic hepatic insufficiency, administration of cethromycin should be closely monitored in this population.

The effect of mild or moderate renal impairment or the effect of hemodialysis on the pharmacokinetic profile of cethromycin was not studied. Subjects with severe renal impairment (creatinine clearance 10-29 mL/min) had markedly increased (2- to 4-fold) plasma exposures compared to subjects with normal renal function in a clinical study. Similarly, in the Phase I meta-analyses, subjects with severe renal impairment had higher peak exposures and higher total exposures to cethromycin, by factors of 3 to 4. However, given the high variability in cethromycin plasma concentrations, and the lack of an increase in adverse events in subjects with severe renal impairment who had high cethromycin exposures in plasma, dosage adjustment is not recommended for subjects with renal impairment.

6.2.4 Drug-Drug Interactions

6.2.4.1. CYP3A Inducers and Inhibitors: Rifampin and Ketoconazole

Administration of cethromycin with rifampin, a strong CYP3A inducer, resulted in a 95% reduction in cethromycin plasma exposure, and coadministration with ketoconazole, a strong CYP3A4 inhibitor, resulted in a 5-fold increase in cethromycin plasma exposure.

6.2.4.2. CYP3A Substrates: Midazolam and Ethinyl Estradiol

Regarding CYP3A substrates, cethromycin coadministration resulted in a 1.3-fold increase in midazolam exposures, but had no effect on ethinyl estradiol exposures. Therefore, based on the above findings, cautionary use of cethromycin is recommended with other drugs that are CYP3A inhibitors, inducers, or substrates.

6.2.4.3. CYP1A2 Substrates: Theophylline and R-warfarin

Cethromycin did not show significant inhibitory or inductive effects on CYP1A2 activity in either clinical studies (theophylline or R-warfarin) or *in vitro* studies.

6.2.4.4. CYP2C9 Substrate: S-warfarin

Although cethromycin did not show a significant effect on CYP2C9 activity i*n vitro*, coadministration with warfarin resulted in a 17% increase in S-warfarin, a CYP2C9 substrate. Given the narrow and variable therapeutic index of warfarin, the increase in S-warfarin exposure may be of clinical significance, and coagulation tests should be monitored more closely in patients taking concomitant warfarin and cethromycin.

6.2.4.5. CYP2C19, 2D6, and 2E1 Interactions

Cethromycin had no affect on CYP2C19, CYP2D6 or CYP2E1 activity in *in vitro* studies. Therefore, no dosage adjustment is recommended when cethromycin is administered with substrates for any of these CYP isozymes.

6.2.4.6. P-gp Interactions: Vinblastine and Digoxin

In vitro, cethromycin inhibited the P-gp-mediated transport of vinblastine, and *in vivo*, plasma exposures to the P-gp substrate, digoxin, were increased by 31% with cethromycin coadministration *in vivo*. Given the narrow therapeutic window of digoxin, digoxin plasma concentrations should be monitored and doses may need to be lowered when the two medications are administered together.

6.2.4.7. Acid Reducers: Ranitidine and Sucralfate

Pretreatment with the acid-reducer, ranitidine, reduced plasma exposures to cethromycin (≤26%); however, sucralfate pretreatment had no effect on the pharmacokinetic profile of cethromycin. Due to the wide variability in cethromycin plasma exposures, the change in the pharmacokinetic profile of cethromycin following ranitidine treatment is not considered clinically significant; therefore, no dose adjustment with ranitidine or sucralfate treatment is necessary.

7. EFFICACY

The clinical program to support the effectiveness of oral cethromycin 300 mg QD for the treatment of CAP included two active-controlled, double-blind, randomized, parallel-group studies and two uncontrolled double-blind, randomized, parallel-group studies. In addition, two uncontrolled double-blind, randomized, parallel-group bronchitis studies and two uncontrolled double-blind, randomized, parallel-group sinusitis studies provide additional information on eradication of causative pathogens (*S. pneumoniae*, *H. influenzae, S. aureus,* and *M. catarrhalis*).

The primary focus of this briefing book will be the summary of the two active-controlled, double-blind, randomized, parallel-group CAP studies (CL05-001 and CL06-001) conducted by Advanced Life Sciences. Supportive efficacy data will be presented from a Phase II/III uncontrolled double-blind, randomized, parallel-group CAP study (M00-219) and a Phase II uncontrolled double-blind, randomized, parallel-group CAP study (M99-054) conducted by Abbott Laboratories.

7.1. Key Efficacy Studies

7.1.1 Study Design

Studies CL05-001 and CL06-001 were Phase III, double-blind, randomized, parallel-group, multi-center, multi-national comparison studies in subjects with CAP. Subjects were randomly assigned within each study in a 1:1 ratio to one of two treatment arms to receive either cethromycin at a dose of 300 mg QD for 7 days, or clarithromycin at a dose of 250 mg BID for 7 days.

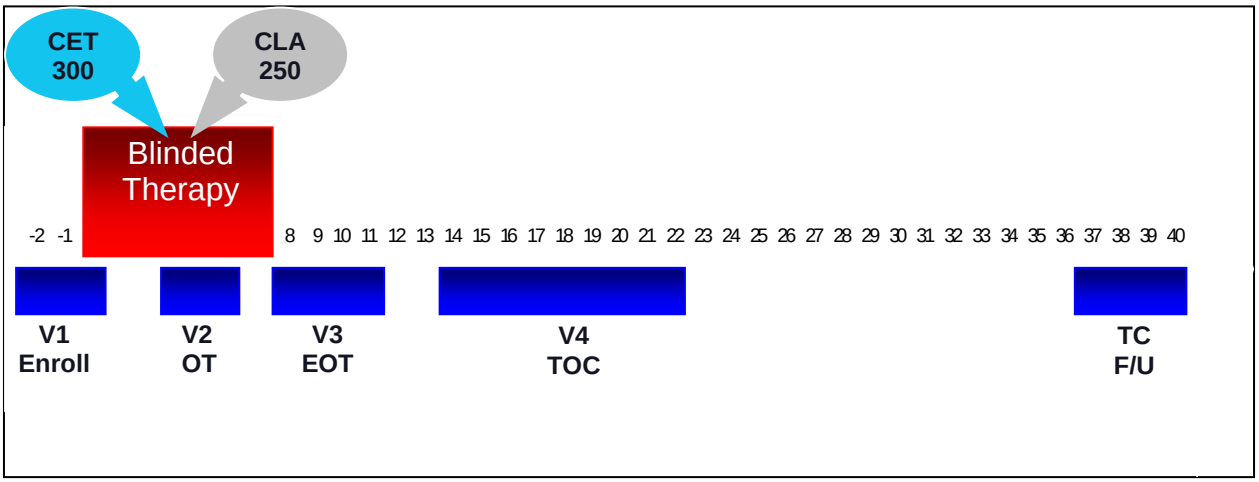
At enrollment, subjects were evaluated for etiologic pathogens (via respiratory and blood cultures, serology, and antigen identification), signs and symptoms of CAP, severity of disease, and acute pulmonary infiltrates via chest x-ray. Eligible subjects could begin study-directed treatment before the results of pretreatment cultures were known, provided that they met the requisite inclusion and exclusion criteria. Inclusion criteria in the two studies were identical and are outlined in Table 19.

Table 19: Inclusion Criteria for Studies CL05-001 and CL06-001

Inclusion Criteria
Ambulatory male or female subjects ≥18 years of age.
Female subjects who were non-lactating and at no risk for pregnancy.
Subject had a chest x-ray consistent with a clinical diagnosis of bacterial pneumonia as interpreted by the radiologist.
Subject was a suitable candidate for oral antibiotic therapy and was able to swallow capsules intact.
The subject presented with a recent respiratory illness which, upon consideration of the signs and symptoms after physical examination, was consistent with the diagnosis of bacterial CAP. Subjects requiring immediate study drug therapy before culture results were known could be entered with a presumptive diagnosis based on a chest radiograph which demonstrated a new pulmonary infiltrate(s) and at least two of the following categories of signs and symptoms: • cough; • fever (oral temperature >38.0°C or >100.4°F or equivalent tympanic or rectal temperature); • development of, or increase in, dyspnea or tachypnea (elevated respiratory rate ≥20/min); • auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (i.e., dullness on percussion, bronchial breath sounds [crackles, rhonchi, wheezes, or egophony]); • an elevated total peripheral white blood cell count (WBC >10,000/mm^3); or >15% immature neutrophils (bands), regardless of total peripheral WBC count; or leukopenia with WBC <4,500/mm^3 supported inclusion of the subject into the study.
Subjects were required to have specimens collected for microbiological documentation within 48 hours prior to enrollment. Specimens included: • Mucopurulent or purulent respiratory/sputum sample for testing via Gram stain, culture, and susceptibility testing; • Blood samples for culture of typical aerobic microorganisms (aerobic bottle only, x 2 samples) and serology for atypical pathogens (*L. pneumophila, M. pneumoniae,* and *C. pneumoniae*); • Urine sample for antigen detection of *L. pneumophila*.
Written, voluntary informed consent was obtained from the subject (or legal representative) prior to initiation of any study related procedures.

As shown in Figure 6, evaluations were performed within 4-6 days post-initiation of therapy (Evaluation 2/Days 4-6), 24-72 hours after the last dose (Evaluation 3/Days 8-11), and again at 7-14 days after taking the last dose of study medication (Evaluation 4/Days 14-22 – Test-of-Cure). Each subject received a follow-up telephone call at 30-33 days after taking the last dose of study medication (Evaluation 5/Days 37-40).

Figure 6: Studies CL05-001 and CL06-001: Graphical Schedule of Visits



CET = cethromycin; CLA = clarithromycin; V=Visit or Evaluation; OT = On Therapy; EOT = End of Therapy; TOC = Test of Cure; TC F/U= Telephone follow-up

Enrolled subjects could be hospitalized during the course of study for the purpose of ensuring compliance with study procedures, or if hospitalization was the standard of medical care.

7.1.2 Efficacy Endpoints

7.1.2.1. Primary Efficacy Endpoint

In Studies CL05-001 and CL06-001, clinical outcome was the primary variable for the indication of CAP. The investigator compared the clinical findings and chest x-ray results at Evaluation 4 to the findings prior to study treatment (Evaluation 1) for each subject and assigned a clinical response. Bacteriology was not considered a factor when evaluating clinical response. The clinical outcome is defined in Table 20.

Table 20: Investigator Assignment of Clinical Response in Studies CL05-001 and CL06-001

Clinical Response	Definition
Clinical Cure (applicable for Evaluation 4 Days 14-22)	Improvement or return to pre-infection state or lack of progression in all pulmonary infiltrates originally consistent with pneumonia on chest radiograph AND Resolution of all signs and symptoms of CAP originally present at time of enrollment.
Clinical Failure (applicable for all Evaluations)	The subject was considered to be a therapy failure under the following conditions: • Persistence or worsening in signs or symptoms of the acute process after 3 to 5 days of therapy or requirement of additional antibiotic for initial pneumonia due to lack of improvement; • Development of new pulmonary infection or extrapulmonary infection requiring antimicrobial therapy other than, or in addition to, the study medication; • Progression of chest radiological abnormalities; • Death due to pneumonia.
Indeterminate (applicable for Evaluation 4 or at premature discontinuation)	The evaluation was not possible (e.g., lost to follow-up, disallowed medication use, premature discontinuation due to an adverse event, intercurrent illness, or major protocol violation); the reason was to be recorded on the case report form.

The clinical cure rate at the Test-of-Cure Visit was the primary efficacy endpoint and was defined as the percentage of subjects who had a clinical response of "Clinical Cure."

7.1.2.2. Supportive Efficacy Endpoints

The supportive efficacy variables included in this overview are the bacteriological cure rate, bacteriological eradication rate, pathogen eradication rate, and radiological success rate.

Bacterial Response Definitions. The bacteriological response was assigned by Advanced Life Sciences for each qualifying pathogen by assessing the culture, serologic, and/or antigen test results at appropriate evaluation visits. The response categories for evaluation of culture results are summarized in Table 21.

Table 21: Assignment of Bacteriological Response in Studies CL05-001 and CL06-001

Bacteriological Response	Definition
Presumed Eradication[a]	In the absence of a repeat culture, the initial pathogen(s) were presumptively eradicated if the definition of clinical cure was met.
Eradication	The absence of the original pathogen(s) from a repeat culture performed at Evaluation 4.
Colonization	Isolation of an organism culture in an asymptomatic subject.
Presumed Persistence[a]	In the absence of a repeat culture, the original pathogen(s) were presumed persistent if the definition of clinical failure was met.
Persistence	The presence of the original pathogen(s) in Evaluation 4 culture(s) or at the time of premature discontinuation.
Superinfection	Presence of a new pathogen(s) in a symptomatic subject while subject was on therapy.
Recurrence	Isolation of the original pathogen(s) from a culture taken after Evaluation 4.
New Infection	Isolation of a new pathogen from a culture taken post-treatment in a symptomatic subject.
Indeterminate	The evaluation was not possible (e.g., subject did not return).

a Includes *M. pneumoniae*, *C. pneumoniae,* and *L. pneumophila* according to diagnostic criteria for atypical pathogens

Three bacteriological outcomes (the bacteriological eradication rate, the pathogen eradication rate, and the bacteriological cure rate) were analyzed and defined according to the criteria in Table 22.

Table 22: Definitions of Bacteriological Outcomes in Studies CL05-001 and CL06-001

Response Variable	Definition
The Bacteriological Eradication Rate	For each qualified pathogen, the percentage of subjects from whom the pathogen was eradicated or presumed eradicated.
The Pathogen Eradication Rate	The percentage of all qualifying pathogens eradicated or presumed eradicated (regardless of number of subjects).
The Bacteriological Cure Rate	The percentage of bacteriologically evaluable subjects (i.e., subjects with ≥1 evaluable pathogen) who showed eradication or presumed eradication of all qualifying pathogens.

Serology findings were considered to be supporting evidence of infection if the diagnostic criteria were met.

Radiological Response Definitions. The investigator compared chest x-ray findings obtained at Evaluation 4 (Test-of-Cure Visit) to the findings at Evaluation 1 (pretreatment). Chest x-ray findings obtained (if clinically indicated) at Evaluations 2 and 3 were also compared to Evaluation 1 findings. The radiological response was rated using the definitions summarized in Table 23.

Table 23: Investigator Assignment of Radiological Response in Studies CL05-001 and CL06-001

Radiological Response[a]	Definition
Resolution	Complete clearing of chest x-ray evidence of pneumonia.
Improvement	Reduction in the chest x-ray evidence of pneumonia in comparison to the pretreatment x-ray.
Unchanged	No change in the chest x-ray evidence of pneumonia in comparison to the pretreatment x-ray.
Worsening	Worsening of the chest x-ray evidence of pneumonia in comparison to the pretreatment x-ray.
Indeterminate	The evaluation was not possible (e.g., no follow-up x-ray, etc.).

a Based upon radiologist's interpretation of chest radiograph.

7.1.3 Key Statistical Considerations

7.1.3.1. Analysis Populations

The ITT population was defined as all subjects who received ≥1 dose of study medication and had a clinical diagnosis consistent with bacterial CAP confirmed by a positive pretreatment chest x-ray and appropriate signs/symptoms. All analyses of efficacy were conducted on the ITT population.

The per-protocol clinical (PPc) population was defined as all subjects who met the criteria for ITT evaluability as well as additional criteria for clinical evaluability. All analyses of efficacy were conducted on the PPc population. The requirements for clinical evaluability were as follows:

- The minimum duration of therapy required to qualify for the efficacy evaluation as a failure was 3 days of prescribed study medication and for the efficacy evaluation to qualify as a cure was 80% of prescribed study medication taken;
- No other systemic antimicrobial agent was administered during the period from 2 weeks (4 weeks if long-acting) prior to the start of study drug until Evaluation 4, unless the subject was considered a study treatment failure or had an intercurrent illness and was indeterminate;
- No other major protocol violations.

The per-protocol clinical and bacteriological (PPb) population was defined to be all subjects who met the criteria for clinical evaluability as well as an additional criterion for bacteriological evaluability. As a supportive analysis, the analyses of efficacy were conducted on the PPb population. The requirement for clinical and bacteriological evaluability was:

- At least 1 specific pathogen (*S. pneumoniae*, *H. influenzae*, *S. aureus*, *M. catarrhalis*, or other targeted pathogen) was isolated with significant growth from a valid Evaluation 1 culture or identified via serology (Evaluation 1 and Evaluation 4) or antigen testing.

7.1.3.2. Efficacy Analysis Methods

The primary objective for statistical analysis was to show non-inferiority of cethromycin relative to clarithromycin in the clinical cure rate at the Test-of-Cure Visit.

Non-inferiority was to have been demonstrated when the lower limit of the two-sided 95% confidence interval (CI) for the difference in the clinical cure rate at the Test-of-Cure Visit between treatment groups (cethromycin – clarithromycin) was greater than delta, and included zero, for both the PPc and ITT analyses. Delta was determined by the highest clinical cure rate between the cethromycin treatment group and the clarithromycin treatment group, as follows:

Highest cure rate:	**Delta:**
Greater than or equal to 90%	-10%
Greater than or equal to 80% and less than 90%	-15%
Greater than or equal to 70% and less than 80%	-20%

The CI for the difference in the clinical cure rate at the Test-of-Cure Visit was computed using a normal approximation for the binomial distribution with continuity correction method, $CC = (2 \min(N1, N2))^{-1}$ where N1 was the number of subjects treated with cethromycin and N2 was the number of subjects treated with clarithromycin. In this analysis, any subjects with missing or otherwise indeterminate outcomes were imputed as "Clinical Failure" outcomes. In addition, the clinical cure rates were compared using Fisher's exact test. An exact binomial 95% two-sided CI was provided for the clinical cure rate in each of the 2 treatment groups.

As a supportive analysis of the robustness of the test to the various choices of imputation, the primary analysis was repeated with all missing or otherwise indeterminate outcomes removed from the analysis and repeated again with all missing or otherwise indeterminate outcomes imputed as "Clinical Cures".

The bacteriological cure rates, bacteriological eradication rates, and radiological success rates were analyzed in the same manner as the primary analysis for the clinical cure rate. The summary of pathogen eradication rates were analyzed in the same manner as the primary analysis for the clinical cure rate, except that the analysis used individual pathogens as the primary unit, rather than individual subject.

7.1.4 Results for Studies CL05-001 and CL06-001

7.1.4.1. Disposition

In the integrated analysis, a total of 552 (99.8%) subjects received at least 1 dose of cethromycin 300 mg QD and 551 (99.6%) subjects received at least 1 dose of clarithromycin 250 mg BID. The proportions of subjects who completed study were similar between the treatment groups (cethromycin: 89.7%, clarithromycin: 90.8%). No important treatment group differences were noted for primary reasons for premature discontinuation from study.

No major inconsistencies in subject disposition were observed between the 2 individual studies. A summary of subject disposition for Study CL05-001, Study CL06-001, and the integrated analysis is presented in Table 24.

Table 24: Subject Disposition (Study CL05-001, Study CL06-001, and the Integrated Analysis)

Subject Disposition	Study CL05-001		Study CL06-001		Studies CL05-001 and CL06-001 Combined	
	Cethromycin 300 mg QD	Clarithromycin 250 mg BID	Cethromycin 300 mg QD	Clarithromycin 250 mg BID	Cethromycin 300 mg QD	Clarithromycin 250 mg BID
Randomized Subjects	292	292	261	261	553	553
Randomized and Dosed	291 (99.7%)	291 (99.7%)	261 (100%)	260 (99.6%)	552 (99.8%)	551 (99.6%)
Completed Study	254 (87.0%)	264 (90.4%)	242 (92.7%)	238 (91.2%)	496 (89.7%)	502 (90.8%)
Discontinued	38 (13.0%)	28 (9.6%)	19 (7.3%)	23 (8.8%)	57 (10.3%)	51 (9.2%)
Primary Reason for Discontinuation						
Adverse Event	10 (3.4%)	10 (3.4%)	4 (1.5%)	9 (3.4%)	14 (2.5%)	19 (3.4%)
Clinical Failure	8 (2.7%)	4 (1.4%)	8 (3.1%)	5 (1.9%)	16 (2.9%)	9 (1.6%)
Lost to Follow-up	7 (2.4%)	4 (1.4%)	0	0	7 (1.3%)	4 (0.7%)
Withdrew Consent	6 (2.1%)	3 (1.0%)	4 (1.5%)	4 (1.5%)	10 (1.8%)	7 (1.3%)
Other	7 (2.4%)	7 (2.4%)	3 (1.1%)	5 (1.9%)	10 (1.8%)	12 (2.2%)

In the integrated analysis, 78 of the 1103 subjects who were randomized and dosed were excluded from the ITT population because of insufficient radiological evidence of CAP (53 subjects) or confounding disease (25 subjects). Of the 1025 subjects in the ITT population, 154 subjects were excluded from the PPc population because they did not meet the criteria for clinical evaluability or had major protocol violations. Of the 871 subjects in the PPc population, 602 subjects were excluded from the PPb population because the Gram stain was unacceptable or no target pathogen was isolated. No important treatment group differences were noted for the individual reasons for exclusion from any analysis population.

The only notable inconsistency between the 2 individual studies was for exclusion from the ITT population, where Study CL05-001 had a greater number of subjects excluded due to insufficient radiological evidence of CAP compared to Study CL06-001. There were no important treatment group differences for either study.

7.1.4.2. Baseline Characteristics

In the integrated analysis, the age of the subjects in the ITT population ranged from 18 years to 86 years and the mean age was 48.3 years in the cethromycin group and 48.4 years in the clarithromycin group. About half of the subjects were male (cethromycin: 51.9%, clarithromycin: 49.1%) and most were White (cethromycin: 86.7%, clarithromycin: 85.4%). The only statistically significant difference observed between the treatment groups for any of the demographic characteristics in any of the analysis populations was for age categories in the ITT population, where the cethromycin group had more subjects between 25-64 years of age, while the clarithromycin group had more subjects between 18-24 years of age and between 65-74 years of age. Results for the PPc and PPb populations were generally similar to those described for the ITT population.

The only notable inconsistency between the 2 individual studies was for race, where Study CL06-001 had a greater percentage of subjects who were White compared to Study CL05-001. As Study CL05-001 was conducted in the US, Canada, and South Africa and Study CL06-001 was conducted in Latin America, Europe, and Israel, the difference in race was not unexpected due to the different geographic regions in which the studies were conducted. There were no important treatment group differences for either study. Demographic characteristics of the ITT population from Study CL05-001, Study CL06-001, and the integrated analysis are summarized in Table 25.

Table 25: Demographic Characteristics (ITT Population: Study CL05-001, Study CL06-001, and the Integrated Analysis)

Demographic Characteristics	Study CL05-001		Study CL06-001		Studies CL05-001 and CL06-001 Combined	
	Cethromycin 300 mg QD (N=261)	Clarithromycin 250 mg BID (N=254)	Cethromycin 300 mg QD (N=257)	Clarithromycin 250 mg BID (N=253)	Cethromycin 300 mg QD (N=518)	Clarithromycin 250 mg BID (N=507)
Age (years)						
Mean (± SD)	48.8 (14.34)	50.5 (16.29)	47.8 (16.93)	46.4 (17.42)	48.3 (15.67)	48.4 (16.97)
Min, Max	20, 84	18, 86	18, 83	18, 86	18, 84	18, 86
Categories[a]						
18-24	6 (2.3%)	19 (7.5%)	27 (10.5%)	35 (13.8%)	33 (6.4%)	54 (10.7%)
25-44	103 (39.5%)	77 (30.3%)	84 (32.7%)	76 (30.0%)	187 (36.1%)	153 (30.2%)
45-64	111 (42.5%)	105 (41.3%)	98 (38.1%)	92 (36.4%)	209 (40.3%)	197 (38.9%)
65-74	27 (10.3%)	34 (13.4%)	35 (13.6%)	42 (16.6%)	62 (12.0%)	76 (15.0%)
≥65	41 (15.7%)	53 (20.9%)	48 (18.7%)	50 (19.8%)	89 (17.2%)	103 (20.3%)
≥75	14 (5.4%)	19 (7.5%)	13 (5.1%)	8 (3.2%)	27 (5.2%)	27 (5.3%)
Gender						
Male	133 (51.0%)	126 (49.6%)	136 (52.9%)	123 (48.6%)	269 (51.9%)	249 (49.1%)
Female	128 (49.0%)	128 (50.4%)	121 (47.1%)	130 (51.4%)	249 (48.1%)	258 (50.9%)
Race						
White	210 (80.5%)	199 (78.3%)	239 (93.0%)	234 (92.5%)	449 (86.7%)	433 (85.4%)
Black	31 (11.9%)	27 (10.6%)	1 (0.4%)	1 (0.4%)	32 (6.2%)	28 (5.5%)
Asian	12 (4.6%)	17 (6.7%)	1 (0.4%)	0	13 (2.5%)	17 (3.4%)
AI / AN	0	1 (0.4%)	0	0	0	1 (0.2%)
Other	8 (3.1%)	10 (3.9%)	16 (6.2%)	18 (7.1%)	24 (4.6%)	28 (5.5%)
Region						
Non-US	147 (56.3%)	136 (53.5%)	257 (100%)	253 (100%)	404 (78.0%)	389 (76.7%)
US	114 (43.7%)	118 (46.5%)	NA	NA	114 (22.0%)	118 (23.3%)

ITT=Intent-to-Treat; SD=standard deviation; Min, Max=minimum, maximum; AI/AN=American Indian/Alaska Native; NA=not applicable

a p=0.0380 for treatment group difference using a two-sided Fisher's exact test.

There were no important treatment group differences for weight, body mass index (BMI), ethnicity, tobacco use, or alcohol use in either the integrated analysis or between the 2 individual studies.

In the integrated analysis, the majority of the subjects in the ITT population in both treatment groups (cethromycin: 96.7%, clarithromycin: 98.2%) were determined to be at low risk of mortality according to Fine criteria (I, II, or III). The percentage of subjects who were determined to be at moderate risk of mortality (Fine criteria IV) was slightly higher in the cethromycin (3.3%) group compared with the clarithromycin (1.8%) group. There were no statistically significant differences between the treatment groups in the distribution of subjects by baseline Fine criteria in any of the analysis populations. Results for the PPc and PPb populations were generally similar to those described for the ITT population.

No major inconsistencies in Fine criteria were observed between the 2 individual studies. Subjects in the ITT population are summarized by Fine criteria for Study CL05-001, Study CL06-001, and the integrated analysis in Table 26.

Table 26: Fine Criteria (ITT Population: Study CL05-001, Study CL06-001, and the Integrated Analysis)

	Study CL05-001		Study Cl06-001		Studies CL05-001 and CL06-001 Combined	
Fine Criteria	Cethromycin 300 mg QD (N=261)	Clarithromycin 250 mg BID (N=254)	Cethromycin 300 mg QD (N=257)	Clarithromycin 250 mg BID (N=253)	Cethromycin 300 mg QD (N=518)	Clarithromycin 250 mg BID (N=507)
Risk Class I	136 (52.1%)	110 (43.3%)	126 (49.0%)	132 (52.2%)	262 (50.6%)	242 (47.7%)
Risk Class II	101 (38.7%)	117 (46.1%)	99 (38.5%)	91 (36.0%)	200 (38.6%)	208 (41.0%)
Risk Class III	16 (6.1%)	24 (9.4%)	23 (8.9%)	24 (9.5%)	39 (7.5%)	48 (9.5%)
Risk Class IV	8 (3.1%)	3 (1.2%)	9 (3.5%)	6 (2.4%)	17 (3.3%)	9 (1.8%)

ITT=Intent-to-Treat

In the integrated analysis, the most common pretreatment clinical signs and symptoms were moderate to severe cough, mucopurulent sputum, tachypnea, mild to moderate dyspnea, and rales/crackling. No statistically significant differences were observed between the treatment groups for any of the pretreatment clinical signs and symptoms in the ITT or PPc analysis populations. A statistically significant treatment group difference was observed in the PPb analysis population for cough, which appeared to be more severe in a higher percentage of subjects in the cethromycin group (30.7%) than in the clarithromycin group (18.2%). Results for the PPc and PPb populations were generally similar to those described for the ITT population**.**

Notable inconsistencies between the 2 individual studies included the presence of dyspnea, rhonchi/wheezing, pleuritic chest pain, and fever, where Study CL05-001 had greater percentages of subjects who had dyspnea (reported as mild, moderate, or severe), rhonchi/wheezing, and pleuritic chest pain at baseline and Study CL06-001 had a greater percentage of subjects who had fever at baseline. There were no important treatment group differences for either study. Baseline pretreatment clinical signs and symptoms of the ITT population from Study CL05-001, Study CL06-001, and the integrated analysis are summarized in Table 27.

Table 27: Pretreatment Clinical Signs and Symptoms (ITT Population: Study CL05-001, Study CL06-001, and the Integrated Analysis)

	Study CL05-001		Study CL06-001		Studies CL05-001 and CL06-001 Combined	
Sign / Symptom	Cethromycin 300 mg QD (N=261)	Clarithromycin 250 mg BID (N=254)	Cethromycin 300 mg QD (N=257)	Clarithromycin 250 mg BID (N=253)	Cethromycin 300 mg QD (N=518)	Clarithromycin 250 mg BID (N=507)
Cough						
Absent	0	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.2%)	2 (0.4%)
Mild	28 (10.7%)	31 (12.2%)	28 (10.9%)	25 (9.9%)	56 (10.8%)	56 (11.0%)
Moderate	156 (59.8%)	169 (66.5%)	175 (68.1%)	178 (70.4%)	331 (63.9%)	347 (68.4%)
Severe	77 (29.5%)	53 (20.9%)	53 (20.6%)	49 (19.4%)	130 (25.1%)	102 (20.1%)
Sputum Production						
Present	261 (100%)	253 (99.6%)	257 (100%)	253 (100%)	518 (100%)	506 (99.8%)
Mucopurulent						
Present	155 (59.4%)	151 (59.4%)	169 (65.8%)	180 (71.1%)	324 (62.5%)	331 (65.3%)
Purulent						
Present	105 (40.2%)	101 (39.8%)	87 (33.9%)	72 (28.5%)	192 (37.1%)	173 (34.1%)
Hemoptic						
Present	18 (6.9%)	17 (6.7%)	6 (2.3%)	13 (5.1%)	24 (4.6%)	30 (5.9%)
Tachypnea						
Present	161 (61.7%)	147 (57.9%)	171 (66.5%)	164 (64.8%)	332 (64.1%)	311 (61.3%)
Dyspnea						
Absent	22 (8.4%)	19 (7.5%)	99 (38.5%)	96 (37.9%)	121 (23.4%)	115 (22.7%)
Mild	122 (46.7%)	142 (55.9%)	105 (40.9%)	95 (37.5%)	227 (43.8%)	237 (46.7%)
Moderate	113 (43.3%)	90 (35.4%)	52 (20.2%)	59 (23.3%)	165 (31.9%)	149 (29.4%)
Severe	4 (1.5%)	3 (1.2%)	1 (0.4%)	3 (1.2%)	5 (1.0%)	6 (1.2%)
Rales/Crackling						
Present	229 (87.7%)	222 (87.4%)	238 (92.6%)	238 (94.1%)	467 (90.2%)	460 (90.7%)
Rhonchi/Wheezing						
Present	207 (79.3%)	187 (73.6%)	97 (37.7%)	97 (38.3%)	304 (58.7%)	284 (56.0%)
Egophony and/or Dullness						
Present	141 (54.0%)	151 (59.4%)	110 (42.8%)	105 (41.5%)	251 (48.5%)	256 (50.5%)
Rigors or Shaking Chills						
Present	168 (64.4%)	136 (53.5%)	113 (44.0%)	114 (45.1%)	281 (54.2%)	250 (49.3%)
Pleuritic Chest Pain						
Present	189 (72.4%)	180 (70.9%)	105 (40.9%)	92 (36.4%)	294 (56.8%)	272 (53.6%)
Fever (oral: >38.0ºC or 100.4ºF)						
Present	103 (39.5%)	98 (38.6%)	164 (63.8%)	174 (68.8%)	267 (51.5%)	272 (53.6%)
Missing	0	0	1 (0.4%)	0	1 (0.2%)	0

ITT=Intent-to-Treat

7.1.4.3. Efficacy Results

Efficacy data from the 2 pivotal, controlled CAP studies (CL05-001 and CL06-001) were combined and are summarized as an integrated analysis. Additionally, results of each study are presented individually to illustrate replication of findings.

Clinical Cure Rate

The primary efficacy endpoint for both studies was the clinical cure rate (defined as the percentage of subjects who had a clinical response of "Clinical Cure") at the Test-of-Cure Visit. The primary objective was to demonstrate non-inferiority of cethromycin relative to clarithromycin for the clinical cure rate in both the ITT and PPc populations (co-primary analyses).

The integrated analysis met the primary endpoint for clinical cure rate in both the ITT and PPc populations. In the ITT population, the clinical cure rate was 83.0% in the cethromycin group compared with 84.8% in the clarithromycin group. Based on the 84.8% clinical cure rate for clarithromycin being between 80% and 90%, a delta value of -15% or less on the lower bound and greater than zero on the upper bound [95% CI: -6.4%, +2.8%] established non-inferiority. In the PPc population, the clinical cure rate was 92.8% in the cethromycin group compared with 94.9% in the clarithromycin group. Based on the 94.9% clinical cure rate for clarithromycin being ≥90%, a delta value of -10% or less on the lower bound and greater than zero on the upper bound [95% CI: -5.4%, +1.2%] established non-inferiority.

Comparisons using Fisher's exact test supported non-inferiority ($p>0.05$) in both analysis populations (ITT: $p=0.4454$; PPc: $p=0.2086$). Analyses repeated using various imputation methods for missing data supported the results of the primary efficacy analysis.

No major inconsistencies in clinical cure rate were observed between the 2 individual studies and each study met the protocol-defined non-inferiority criteria. A summary of the clinical cure rates at the Test-of-Cure Visit for the ITT and PPc populations from Study CL05-001, Study CL06-001, and for the integrated analysis is presented in Table 28.

Table 28: Clinical Cure Rate (ITT and PPc Populations: Study CL05-001, Study CL06-001, and the Integrated Analysis)

	Study CL05-001		Study CL06-001	
	Cethromycin 300 mg QD	**Clarithromycin 250 mg BID**	**Cethromycin 300 mg QD**	**Clarithromycin 250 mg BID**
ITT Population[a]				
Clinical Cure Rates	217/261 (83.1%)	206/254 (81.1%)	213/257 (82.9%)	224/253 (88.5%)
CI for Clinical Cure Rates[b]	(78.0%, 87.5%)	(75.7%, 85.7%)	(77.7%, 87.3%)	(84.0%, 92.2%)
Difference in Rates (Ceth–Clari)	2.0%		-5.7%	
CI for Difference in Rates[c]	(-4.8%, 8.9%)		(-11.9%, 0.6%)	
Fisher's Exact Test	0.5667		0.0769	
PPc Population				
Clinical Cure Rates	205/218 (94.0%)	195/208 (93.8%)	205/224 (91.5%)	212/221 (95.9%)
CI for Clinical Cure Rates[b]	(90.0%, 96.8%)	(89.5%, 96.6%)	(87.1%, 94.8%)	(92.4%, 98.1%)
Difference in Rates (Ceth–Clari)	0.3%		-4.4%	
CI for Difference in Rates[c]	(-4.5%, 5.1%)		(-9.1%, 0.3%)	
Fisher's Exact Test	>0.9999		0.0775	

	Integrated Analysis: Studies CL05-001 and CL06-001 Combined	
	Cethromycin 300 mg QD	**Clarithromycin 250 mg BID**
ITT Population[a]		
Clinical Cure Rates	430/518 (83.0%)	430/507 (84.8%)
CI for Clinical Cure Rates[d]	(79.5%, 86.1%)	(81.4%, 87.8%)
Difference in Rates (Ceth–Clari)	-1.8%	
CI for Difference in Rates[c]	(-6.4%, 2.8%)	
Fisher's Exact Test	0.4454	
PPc Population		
Clinical Cure Rate	410/442 (92.8%)	407/429 (94.9%)
CI for Clinical Cure Rates[d]	(89.9%, 95.0%)	(92.3%, 96.8%)
Difference in Rates (Ceth–Clari)	-2.1%	
CI for Difference in Rates[c]	(-5.4%, 1.2%)	
Fisher's Exact Test	0.2086	

ITT=Intent-to-Treat; PPc=Per-Protocol clinical; CI=confidence interval; Ceth=cethromycin; Clari=clarithromycin

a Subjects with 'indeterminate' or 'missing/not done' outcomes were treated as clinical failures in the analyses of the ITT population.

b The 95% CI was computed using the incomplete beta function to give exactly 95% confidence.

c The 95% CI was computed using normal approximation for the binomial distribution with continuity correction method, CC=1/(2 min (N1, N2)) where N1 is the number of subjects treated with cethromycin and N2 is the number of subjects treated with clarithromycin.

d The 95% CI was computed from an exact binomial distribution.

Bacteriological Cure Rate

The bacteriological cure rate was defined as the percentage of bacteriologically evaluable subjects (i.e., subjects with at least 1 evaluable pathogen) who showed eradication of all evaluable pathogens.

In the integrated analysis, the bacteriological cure rate in the ITT population was 86.0% for both the cethromycin and clarithromycin treatment groups [95% CI: -8.0%, +8.0%] ($p>0.9999$). In the PPc population, the bacteriological cure rate was similar between the cethromycin (92.7%) and clarithromycin (96.2%) treatment groups [95% CI: -9.3%, +2.3%] ($p=0.2891$). Analyses repeated using various imputation methods for missing data supported the results observed in both the ITT and PPc populations.

There was a notable inconsistency in the treatment difference for bacteriological cure rate between the 2 individual studies, where cethromycin was numerically superior in Study CL05-001 and clarithromycin was numerically superior in Study CL06-001. These treatment group differences were not statistically significant within the studies. A summary of the bacteriological cure rates at the Test-of-Cure Visit for the ITT and PPc populations from Study CL05-001, Study CL06-001, and the integrated analysis is presented in Table 29.

Table 29: Bacteriological Cure Rate (ITT and PPc Populations: Study CL05-001, Study CL06-001, and the Integrated Analysis)

	Study CL05-001		Study CL06-001	
	Cethromycin 300 mg QD	**Clarithromycin 250 mg BID**	**Cethromycin 300 mg QD**	**Clarithromycin 250 mg BID**
ITT Population[a]				
Bacteriological Cure Rates	73/81 (90.1%)	73/85 (85.9%)	62/76 (81.6%)	62/72 (86.1%)
CI for Bacteriological Cure Rates[b]	(81.5%, 95.6%)	(76.6%, 92.5%)	(71.0, 89.5%)	(75.9%, 93.1%)
Difference in Rates (Ceth–Clari)	4.2%		-4.5%	
CI for Difference in Rates[c]	(-6.2%, 14.7%)		(-17.0%, 8.0%)	
Fisher's Exact Test	0.4782		0.5086	
PPc Population				
Bacteriological Cure Rates	71/73 (97.3%)	67/69 (97.1%)	56/64 (87.5%)	60/63 (95.2%)
CI for Bacteriological Cure Rates[b]	(90.5%, 99.7%)	(89.9%, 99.6%)	(76.8%, 94.4%)	(86.7%, 99.0%)
Difference in Rates (Ceth–Clari)	0.2%		-7.7%	
CI for Difference in Rates[c]	(-6.0%, 6.3%)		(-18.2%, 2.7%)	
Fisher's Exact Test	>0.9999		0.2058	
	Integrated Analysis: Studies CL05-001 and CL06-001 Combined			
	Cethromycin 300 mg QD		**Clarithromycin 250 mg BID**	
ITT Population[a]				
Bacteriological Cure Rates	135/157 (86.0%)		135/157 (86.0%)	
CI for Bacteriological Cure Rates[d]	(79.6%, 91.0%)		(79.6%, 91.0%)	
Difference in Rates (Ceth–Clari)	0.0%			
CI for Difference in Rates[c]	(-8.0%, 8.0%)			
Fisher's Exact Test	>0.9999			
PPc Population				
Bacteriological Cure Rates	127/137 (92.7%)		127/132 (96.2%)	
CI for Bacteriological Cure Rates[d]	(87.0%, 96.4%)		(91.4%, 98.8%)	
Difference in Rates (Ceth–Clari)	-3.5%			
CI for Difference in Rates[c]	(-9.3%, 2.3%)			
Fisher's Exact Test	0.2891			

ITT=Intent-to-Treat; PPc=Per-Protocol clinical; CI=confidence interval; Ceth=cethromycin; Clari=clarithromycin

a Subjects with 'indeterminate' or 'missing/not done' outcomes were treated as bacteriological failures in the analyses of the ITT population.

b The 95% CI was computed using the incomplete beta function to give exactly 95% confidence.

c The 95% CI was computed using normal approximation for the binomial distribution with continuity correction method, CC=1/(2 min (N1, N2)) where N1 is the number of subjects treated with cethromycin and N2 is the number of subjects treated with clarithromycin.

d The 95% CI was computed from an exact binomial distribution.

Bacteriological Eradication Rate

The bacteriological eradication rate was defined for each qualified pathogen as the percent of subjects from whom the pathogen was eradicated.

In the integrated analysis, no clinically significant treatment group differences were noted in the eradication rates of the individual pathogens. The most common pathogens were *H. influenzae*, *M. pneumoniae,* and *S. pneumoniae*, with eradication rates ranging from 81.4% to 96.8% in the treatment groups in the ITT population and from 88.9% to 100% in the treatment groups in the PPc population.

Percent eradication by pathogen was variable between treatment groups and the 2 individual studies. Clinical interpretation of these differences is limited because of the small numbers of specific pathogens within each study and treatment. A summary of bacteriological eradication rates at the Test-of-Cure Visit for the ITT and PPc populations from Study CL05-001, Study CL06-001, and the integrated analysis is presented in Table 30.

Table 30: Bacteriological Eradication Rate (ITT and PPc Populations: Study CL05-001, Study CL06-001, and the Integrated Analysis)

	Study CL05-001		Study CL06-001	
	Cethromycin 300 mg QD	Clarithromycin 250 mg BID	Cethromycin 300 mg QD	Clarithromycin 250 mg BID
ITT Population[a]				
S. pneumoniae[b]	10/12 (83.3%)	20/22 (90.9%)	16/19 (84.2%)	8/12 (66.7%)
H. influenzae[c,d]	34/36 (94.4%)	23/28 (82.1%)	23/34 (67.6%)	21/24 (87.5%)
S. aureus[e]	9/14 (64.3%)	13/14 (92.9%)	7/9 (77.8%)	8/11 (72.7%)
M. catarrhalis	3/3 (100%)	6/6 (100%)	2/4 (50.0%)	4/4 (100%)
C. pneumoniae	6/6 (100%)	5/7 (71.4%)	6/6 (100%)	6/6 (100%)
L. pneumophila	4/4 (100%)	3/5 (60.0%)	1/1 (100%)	4/4 (100%)
M. pneumoniae	11/11 (100%)	17/18 (94.4%)	19/20 (95.0%)	20/23 (87.0%)
PPc Population				
S. pneumoniae	9/9 (100%)	17/18 (94.4%)	15/17 (88.2%)	8/10 (80.0%)
H. influenzae	34/35 (97.1%)	20/22 (90.9%)	22/28 (78.6%)	21/24 (87.5%)
S. aureus	9/10 (90.0%)	13/13 (100%)	6/8 (75.0%)	8/9 (88.9%)
M. catarrhalis	2/2 (100%)	6/6 (100%)	2/3 (66.7%)	4/4 (100%)
C. pneumoniae	6/6 (100%)	5/5 (100%)	5/5 (100%)	4/4 (100%)
L. pneumophila	4/4 (100%)	3/3 (100%)	0/0	4/4 (100%)
M. pneumoniae	11/11 (100%)	16/16 (100%)	18/19 (94.7%)	19/19 (100%)

	Integrated Analysis: Studies CL05-001 and CL06-001 Combined	
	Cethromycin 300 mg QD	Clarithromycin 250 mg BID
ITT Population[a]		
S. pneumoniae[b]	26/31 (83.9%)	28/34 (82.4%)
H. influenzae[c,d]	57/70 (81.4%)	44/52 (84.6%)
S. aureus[e]	16/23 (69.6%)	21/25 (84.0%)
M. catarrhalis	5/7 (71.4%)	10/10 (100%)
C. pneumoniae	12/12 (100%)	11/13 (84.6%)
L. pneumophila	5/5 (100%)	7/9 (77.8%)
M. pneumoniae	30/31 (96.8%)	37/41 (90.2%)
PPc Population		
S. pneumoniae	24/26 (92.3%)	25/28 (89.3%)
H. influenzae	56/63 (88.9%)	41/46 (89.1%)
S. aureus	15/18 (83.3%)	21/22 (95.5%)
M. catarrhalis	4/5 (80.0%)	10/10 (100%)
C. pneumoniae	11/11 (100%)	9/9 (100%)
L. pneumophila	4/4 (100%)	7/7 (100%)
M. pneumoniae	29/30 (96.7%)	35/35 (100%)

ITT=Intent-to-Treat; PPc=Per-Protocol clinical

a Subjects with 'indeterminate' or 'missing/not done' outcomes were treated as non-eradication in the analyses of the ITT population.

b One clarithromycin subject is included that had a *S. pneumoniae* pathogen isolated after the initiation of treatment; the subject had an outcome of colonization.

c One cethromycin subject is included that had a *H. influenzae* pathogen isolated after the initiation of treatment; the subject had an outcome of colonization.

d Four clarithromycin subjects are included that had *H. influenzae* pathogens isolated after the initiation of treatment; 2 had outcomes of colonization, 1 had an outcome of superinfection, and 1 had an outcome of new infection.

e One cethromycin subject is included that had a *S. aureus* pathogen isolated after the initiation of treatment; the subject had an outcome of new infection.

Pathogen Eradication Rate

The pathogen eradication rate was defined as the percentage of all qualifying pathogens eradicated from all subjects (regardless of the number of subjects).

For the integrated analysis, the pathogen eradication rate in the ITT population was similar between the cethromycin (85.3%) and clarithromycin (88.3%) treatment groups [95% CI: -10.3%, +4.4%] (p=0.4370). In the PPc population, the pathogen eradication rate was similar between the cethromycin (92.3%) and clarithromycin (97.4%) treatment groups [95% CI: -10.4%, +0.1%] (p=0.0695). Analyses repeated using various imputation methods for missing data supported the results observed in both the ITT and PPc populations.

There was a notable inconsistency in the treatment difference for pathogen eradication rate between the 2 individual studies, where cethromycin and clarithromycin were similar in Study CL05-001 and clarithromycin was numerically superior in Study CL06-001. These treatment group differences were not statistically significant within the studies. A summary of pathogen eradication rates at the Test-of-Cure Visit for the ITT and PPc populations from Study CL05-001, Study CL06-001, and for the integrated analysis is presented in Table 31.

Table 31: Pathogen Eradication Rate (ITT and PPc Populations: Study CL05-001, Study CL06-001, and the Integrated Analysis)

	Study CL05-001		Study CL06-001	
	Cethromycin 300 mg QD	**Clarithromycin 250 mg BID**	**Cethromycin 300 mg QD**	**Clarithromycin 250 mg BID**
ITT Population[a]				
Pathogen Eradication Rates	77/86 (89.5%)	87/98 (88.8%)	74/91 (81.3%)	71/81 (87.7%)
CI for Pathogen Eradication Rates[b]	(81.1%, 95.1%)	(80.8%, 94.3%)	(71.8%, 88.7%)	(78.5%, 93.9%)
Difference in Rates (Ceth–Clari)	0.8%		-6.3%	
CI for Difference in Rates[c]	(-8.8%, 10.3%)		(-17.7%, 5.0%)	
Fisher's Exact Test	>0.9999		0.2975	
PPc Population				
Pathogen Eradication Rate	75/77 (97.4%)	80/81 (98.8%)	68/78 (87.2%)	68/71 (95.8%)
CI for Pathogen Eradication Rates[b]	(90.9%, 99.7%)	(93.3%, 100.0%)	(77.7%, 93.7%)	(88.1%, 99.1%)
Difference in Rates (Ceth–Clari)	-1.4%		-8.6%	
CI for Difference in Rates[c]	(-6.3%, 3.6%)		(-18.1%, 0.9%)	
Fisher's Exact Test	0.6132		0.0828	

	Integrated Analysis: Studies CL05-001 and CL06-001 Combined	
	Cethromycin 300 mg QD	**Clarithromycin 250 mg BID**
ITT Population[a]		
Pathogen Eradication Rates	151/177 (85.3%)	158/179 (88.3%)
CI for Pathogen Eradication Rates[d]	(79.2%, 90.2%)	(82.6%, 92.6%)
Difference in Rates (Ceth–Clari)	-3.0%	
CI for Difference in Rates[c]	(-10.3%, 4.4%)	
Fisher's Exact Test	0.4370	
PPc Population		
Pathogen Eradication Rates	143/155 (92.3%)	148/152 (97.4%)
CI for Pathogen Eradication Rates[d]	(86.9%, 95.9%)	(93.4%, 99.3%)
Difference in Rates (Ceth–Clari)	-5.1%	
CI for Difference in Rates[c]	(-10.4%, 0.1%)	
Fisher's Exact Test	0.0695	

ITT=Intent-to-Treat; PPc=Per-Protocol clinical; CI=confidence interval; Ceth=cethromycin; Clari=clarithromycin

a Isolates with 'indeterminate' or 'missing/not done' outcomes were treated as non-eradication in the analyses of the ITT population.

b The 95% CI was computed using the incomplete beta function to give exactly 95% confidence.

c The 95% CI was computed using normal approximation for the binomial distribution with continuity correction method, CC=1/(2 min (N1, N2)) where N1 is the number of subjects treated with cethromycin and N2 is the number of subjects treated with clarithromycin.

d The 95% CI was computed from an exact binomial distribution.

Radiological Success Rate

The radiological success rate was defined as the percentage of subjects who had a "resolution" or "improvement" in chest x-ray at the Test-of-Cure Visit.

For the integrated analysis, the radiological success (resolution or improvement) rate in the ITT population was similar between the cethromycin (85.3%) and clarithromycin (86.6%) treatment groups [95% CI: -5.6%, +3.1%] (p=0.5902). In the PPc population, the radiological success rate was similar between the cethromycin (93.4%) and clarithromycin (94.2%) treatment groups [95% CI: -4.1%, +2.6%] (p=0.6757). Analyses repeated using various imputation methods for missing data supported the results observed in both the ITT and PPc populations. Results for the PPb population were generally similar to those described for the ITT and PPc populations.

No major inconsistencies in radiological success rate were observed between the 2 individual studies. A summary of radiological success rates at the Test-of-Cure Visit for the ITT and PPc populations from Study CL05-001, Study CL06-001, and the integrated analysis is presented in Table 32.

Table 32: Radiological Success Rate (ITT and PPc Populations: Study CL05-001, Study CL06-001, and the Integrated Analysis)

	Study CL05-001		Study CL06-001	
	Cethromycin 300 mg QD	**Clarithromycin 250 mg BID**	**Cethromycin 300 mg QD**	**Clarithromycin 250 mg BID**
ITT Population[a]				
Radiological Success Rates	215/261 (82.4%)	207/254 (81.5%)	227/257 (88.3%)	232/253 (91.7%)
CI for Radiological Success Rates[b]	(77.2%, 86.8%)	(76.2%, 86.1%)	(83.8%, 92.0%)	(87.6%, 94.8%)
Difference in Rates (Ceth–Clari)	0.9%		-3.4%	
CI for Difference in Rates[c]	(-6.0%, 7.7%)		(-8.8%, 2.0%)	
Fisher's Exact Test	0.8195		0.2383	
PPc Population				
Radiological Success Rates	202/218 (92.7%)	192/208 (92.3%)	211/224 (94.2%)	212/221 (95.9%)
CI Radiological Success Rates[b]	(88.4%, 95.7%)	(87.8%, 95.5%)	(90.3%, 96.9%)	(92.4%, 98.1%)
Difference in Rates (Ceth–Clari)	0.4%		-1.7%	
CI for Difference in Rates[c]	(-4.9%, 5.6%)		(-6.0%, 2.5%)	
Fisher's Exact Test	>0.9999		0.5130	
	Integrated Analysis: Studies CL05-001 and CL06-001 Combined			
	Cethromycin 300 mg QD		**Clarithromycin 250 mg BID**	
ITT Population[a]				
Radiological Success Rates	442/518 (85.3%)		439/507 (86.6%)	
CI for Radiological Success Rates[d]	(82.0%, 88.3%)		(83.3%, 89.4%)	
Difference in Rates (Ceth–Clari)	-1.3%			
CI for Difference in Rates[c]	(-5.6%, 3.1%)			
Fisher's Exact Test	0.5902			
PPc Population				
Radiological Success Rates	413/442 (93.4%)		404/429 (94.2%)	
CI for Radiological Success Rates[d]	(90.7%, 95.6%)		(91.5%, 96.2%)	
Difference in Rates (Ceth–Clari)	-0.7%			
CI for Difference in Rates[c]	(-4.1%, 2.6%)			
Fisher's Exact Test	0.6757			

ITT=Intent-to-Treat; PPc=Per-Protocol clinical; CI=confidence interval; Ceth=cethromycin; Clari=clarithromycin

a Subjects with 'indeterminate' or 'missing/not done' outcomes were treated as radiological failures in the analyses of the ITT population.

b The 95% CI was computed using the incomplete beta function to give exactly 95% confidence.

c The 95% CI was computed using normal approximation for the binomial distribution with continuity correction method, CC=1/(2 min (N1, N2)) where N1 is the number of subjects treated with cethromycin and N2 is the number of subjects treated with clarithromycin.

d The 95% CI was computed from an exact binomial distribution.

7.1.4.4. Additional Analyses

In the integrated analysis, the clinical cure rates were similar between the treatment groups and across the pathogens ranging from 71.4% to 91.7% in the ITT population and from 80.0% to 100% in the PPb population.

Clinical cure rate by pathogen was variable between treatment groups and the 2 individual studies. Clinical interpretation of these differences is limited because of the small numbers of specific pathogens within each study and treatment. The clinical cure rates for target pathogens (*S. pneumoniae*, *H. influenzae*, *S. aureus* and *M. catarrhalis*) are presented for the ITT and PPb populations from Study CL05-001, Study CL06-001, and the integrated analysis in Table 33.

Table 33: Clinical Cure Rate for Target Pathogens Isolated Pretreatment (ITT and PPb Populations: Study CL05-001, Study CL06-001, and the Integrated Analysis)

	Study CL05-001		Study CL06-001	
	Cethromycin 300 mg QD	Clarithromycin 250 mg BID	Cethromycin 300 mg QD	Clarithromycin 250 mg BID
ITT Population[a]				
S. pneumoniae	10/12 (83.3%)	17/22 (77.3%)	15/19 (78.9%)	7/11 (63.6%)
H. influenzae	33/36 (91.7%)	23/26 (88.5%)	24/33 (72.7%)	21/22 (95.5%)
S. aureus	10/14 (71.4%)	13/14 (92.9%)	7/8 (87.5%)	9/11 (81.8%)
M. catarrhalis	3/3 (100%)	6/6 (100%)	2/4 (50.0%)	3/4 (75.0%)
PPb Population				
S. pneumoniae	9/9 (100%)	15/18 (83.3%)	15/17 (88.2%)	7/9 (77.8%)
H. influenzae	33/35 (94.3%)	20/20 (100%)	23/27 (85.2%)	21/22 (95.5%)
S. aureus	9/10 (90.0%)	13/13 (100%)	6/7 (85.7%)	9/9 (100%)
M. catarrhalis	2/2 (100%)	6/6 (100%)	2/3 (66.7%)	3/4 (75.0%)
	Integrated Analysis: Studies CL05-001 and CL06-001 Combined			
	Cethromycin 300 mg QD		Clarithromycin 250 mg BID	
ITT Population[a]				
S. pneumoniae	25/31 (80.6%)		24/33 (72.7%)	
H. influenzae	57/69 (82.6%)		44/48 (91.7%)	
S. aureus	17/22 (77.3%)		22/25 (88.0%)	
M. catarrhalis	5/7 (71.4%)		9/10 (90.0%)	
PPb Population				
S. pneumoniae	24/26 (92.3%)		22/27 (81.5%)	
H. influenzae	56/62 (90.3%)		41/42 (97.6%)	
S. aureus	15/17 (88.2%)		22/22 (100%)	
M. catarrhalis	4/5 (80.0%)		9/10 (90.0%)	

ITT=Intent-to-Treat; PPb=Per-Protocol clinical and bacteriological

a Subjects with 'indeterminate' or 'missing/not done' outcomes were treated as clinical failures in the analyses of the ITT population.

A summary of the pretreatment cethromycin and clarithromycin MIC (μg/mL) distributions for target pathogens in the ITT population for the integrated analysis is presented in Table 34.

Table 34: Pretreatment Cethromycin and Clarithromycin MIC (µg/mL) Distributions for Target Pathogens (ITT Population: Integrated Analysis)

	S. pneumoniae	***H. influenzae***	***S. aureus***	***M. catarrhalis***
Cethromycin				
Number of Isolates	31	69	22	7
MIC (µg/mL) Range	0.004-0.12	0.002-32	0.03->32	0.06-0.25
Clarithromycin				
Number of Isolates	33	48	25	10
MIC (µg/mL) Range	≤0.015->32	0.25->32	0.25->32	0.12-0.25

ITT=Intent-to-Treat; MIC=minimum inhibitory concentration

Results in the PPb population were similar to the ITT population.

Pretreatment MIC distributions versus bacteriological and clinical responses for cethromycin and clarithromycin are provided for the ITT and PPb populations for the integrated analysis. Analyses are not summarized for the 2 studies individually due the small numbers of some pathogens within each study. Summaries are provided for *S. pneumoniae* in Table 35, for *H. influenzae* in Table 36, for *S. aureus* in Table 37, and for *M. catarrhalis* in Table 38. Results suggested a correlation between clinical cure and bacteriological eradication for the target pathogens in both treatment groups. Data from susceptibility testing showed no overall correlation with bacteriological and clinical response.

Table 35: Pretreatment MIC Distributions for *S. pneumoniae* Versus Bacteriological and Clinical Responses for Cethromycin and Clarithromycin (ITT and PPb Populations: Studies CL05-001 and CL06-001 Combined)

MIC[a] (μg/mL)	Bacteriological Response			Clinical Response			Total
	Erad	Persist	Indeter	Cure	Failure	Indeter	
ITT Population							
Cethromycin 300 mg QD							
0.004	1 (100%)	0	0	1 (100%)	0	0	1
0.008	7 (87.5%)	1 (12.5%)	0	7 (87.5%)	1 (12.5%)	0	8
0.015	13 (81.3%)	1 (6.3%)	2 (12.5%)	12 (75.0%)	1 (6.3%)	3 (18.8%)	16
0.03	5 (100%)	0	0	5 (100%)	0	0	5
0.12	0	0	1 (100%)	0	0	1 (100%)	1
Total	26	2	3	25	2	4	31
Clarithromycin 250 mg BID							
≤0.015	1 (100%)	0	0	0	1 (100%)	0	1
0.03	4 (100%)	0	0	4 (100%)	0	0	4
0.06	15 (83.3%)	2 (11.1%)	1 (5.6%)	12 (66.7%)	4 (22.2%)	2 (11.1%)	18
0.25	1 (100%)	0	0	1 (100%)	0	0	1
2	1 (100%)	0	0	1 (100%)	0	0	1
4	1 (100%)	0	0	1 (100%)	0	0	1
8	1 (100%)	0	0	1 (100%)	0	0	1
>32	2 (66.7%)	0	1 (33.3%)	2 (66.7%)	0	1 (33.3%)	3
Missing	2 (66.7%)	0	1 (33.3%)	2 (66.7%)	0	1 (33.3%)	3
Total	28	2	3	24	5	4	33
PPb Population							
Cethromycin 300 mg QD							
0.004	1 (100%)	0	0	1 (100%)	0	0	1
0.008	7 (87.5%)	1 (12.5%)	0	7 (87.5%)	1 (12.5%)	0	8
0.015	12 (92.3%)	1 (7.7%)	0	12 (92.3%)	1 (7.7%)	0	13
0.03	4 (100%)	0	0	4 (100%)	0	0	4
Total	24	2	0	24	2	0	26
Clarithromycin 250 mg BID							
≤0.015	1 (100%)	0	0	0	1 (100%)	0	1
0.03	4 (100%)	0	0	4 (100%)	0	0	4
0.06	13 (86.7%)	2 (13.3%)	0	11 (73.3%)	4 (26.7%)	0	15
0.25	1 (100%)	0	0	1 (100%)	0	0	1
2	1 (100%)	0	0	1 (100%)	0	0	1
4	1 (100%)	0	0	1 (100%)	0	0	1
>32	2 (100%)	0	0	2 (100%)	0	0	2
Missing	2 (100%)	0	0	2 (100%)	0	0	2
Total	25	2	0	22	5	0	27

ITT=Intent-to-Treat; PPb=Per-Protocol clinical and bacteriological; MIC=minimum inhibitory concentration; Erad=eradication; Persist=persistence; Indeter=indeterminate

Missing=susceptibility test was not performed.

Presumed eradication was collapsed with eradication. Presumed persistence was collapsed with persistence.

a Pretreatment MIC assessment was made on or before Day 1.

Table 36: Pretreatment MIC Distributions for *H. influenzae* Versus Bacteriological and Clinical Responses for Cethromycin and Clarithromycin (ITT and PPb Populations: Studies CL05-001 and CL06-001 Combined)

MIC[a] (µg/mL)	Bacteriological Response				Clinical Response			Total
	Erad	Persist	Col	Indeter	Cure	Failure	Indeter	
ITT Population								
Cethromycin 300 mg QD								
0.002	1 (100%)	0	0	0	1 (100%)	0	0	1
0.5	2 (100%)	0	0	0	2 (100%)	0	0	2
1	7 (77.8%)	1 (11.1%)	0	1 (11.1%)	7 (77.8%)	1 (11.1%)	1 (11.1%)	9
2	23 (82.1%)	3 (10.7%)	1 (3.6%)	1 (3.6%)	24 (85.7%)	3 (10.7%)	1 (3.6%)	28
4	16 (88.9%)	0	0	2 (11.1%)	16 (88.9%)	0	2 (11.1%)	18
8	5 (100%)	0	0	0	4 (80.0%)	1 (20.0%)	0	5
32	1 (100%)	0	0	0	1 (100%)	0	0	1
Missing	2 (40.0%)	1 (20.0%)	0	2 (40.0%)	2 (40.0%)	1 (20.0%)	2 (40.0%)	5
Total	57	5	1	6	57	6	6	69
Clarithromycin 250 mg BID								
0.25	0	0	0	1 (100%)	0	0	1 (100%)	1
0.5	1 (100%)	0	0	0	1 (100%)	0	0	1
4	7 (100%)	0	0	0	7 (100%)	0	0	7
8	21 (87.5%)	1 (4.2%)	0	2 (8.3%)	21 (87.5%)	1 (4.2%)	2 (8.3%)	24
16	10 (100%)	0	0	0	10 (100%)	0	0	10
32	3 (100%)	0	0	0	3 (100%)	0	0	3
>32	1 (100%)	0	0	0	1 (100%)	0	0	1
Missing	1 (100%)	0	0	0	1 (100%)	0	0	1
Total	44	1	0	3	44	1	3	48
PPb Population								
Cethromycin 300 mg QD								
0.002	1 (100%)	0	0	0	1 (100%)	0	0	1
0.5	2 (100%)	0	0	0	2 (100%)	0	0	2
1	7 (87.5%)	1 (12.5%)	0	0	7 (87.5%)	1 (12.5%)	0	8
2	23 (85.2%)	3 (11.1%)	1 (3.7%)	0	24 (88.9%)	3 (11.1%)	0	27
4	15 (100%)	0	0	0	15 (100%)	0	0	15
8	5 (100%)	0	0	0	4 (80.0%)	1 (20.0%)	0	5
32	1 (100%)	0	0	0	1 (100%)	0	0	1
Missing	2 (66.7%)	1 (33.3%)	0	0	2 (66.7%)	1 (33.3%)	0	3
Total	56	5	1	0	56	6	0	62
Clarithromycin 250 mg BID								
0.5	1 (100%)	0	0	0	1 (100%)	0	0	1
4	7 (100%)	0	0	0	7 (100%)	0	0	7
8	20 (95.2%)	1 (4.8%)	0	0	20 (95.2%)	1 (4.8%)	0	21
16	9 (100%)	0	0	0	9 (100%)	0	0	9
32	2 (100%)	0	0	0	2 (100%)	0	0	2
>32	1 (100%)	0	0	0	1 (100%)	0	0	1
Missing	1 (100%)	0	0	0	1 (100%)	0	0	1
Total	41	1	0	0	41	1	0	42

ITT=Intent-to-Treat; PPb=Per-Protocol clinical and bacteriological; MIC=minimum inhibitory concentration; Erad=eradication; Persist=persistence; Col=colonization; Indeter=indeterminate

Missing=susceptibility test was not performed.

Presumed eradication was collapsed with eradication. Presumed persistence was collapsed with persistence.

a Pretreatment MIC assessment was made on or before Day 1.

Table 37: Pretreatment MIC Distributions for *S. aureus* Versus Bacteriological and Clinical Responses for Cethromycin and Clarithromycin (ITT and PPb Populations: Studies CL05-001 and CL06-001 Combined)

MIC[a] (μg/mL)	Bacteriological Response				Clinical Response			Total
	Erad	Persist	Col	Indeter	Cure	Failure	Indeter	
ITT Population								
Cethromycin 300 mg QD								
0.03	1 (100%)	0	0	0	1 (100%)	0	0	1
0.06	14 (73.7%)	2 (10.5%)	1 (5.3%)	2 (10.5%)	15 (78.9%)	2 (10.5%)	2 (10.5%)	19
0.12	1 (100%)	0	0	0	1 (100%)	0	0	1
>32	0	0	0	1 (100%)	0	0	1 (100%)	1
Total	16	2	1	3	17	2	3	22
Clarithromycin 250 mg BID								
0.25	10 (83.3%)	0	1 (8.3%)	1 (8.3%)	11 (91.7%)	0	1 (8.3%)	12
0.5	10 (90.9%)	0	0	1 (9.1%)	10 (90.9%)	0	1 (9.1%)	11
8	0	0	0	1 (100%)	0	0	1 (100%)	1
>32	1 (100%)	0	0	0	1 (100%)	0	0	1
Total	21	0	1	3	22	0	3	25
PPb Population								
Cethromycin 300 mg QD								
0.03	1 (100%)	0	0	0	1 (100%)	0	0	1
0.06	13 (86.7%)	2 (13.3%)	0	0	13 (86.7%)	2 (13.3%)	0	15
0.12	1 (100%)	0	0	0	1 (100%)	0	0	1
Total	15	2	0	0	15	2	0	17
Clarithromycin 250 mg BID								
0.25	10 (90.9%)	0	1 (9.1%)	0	11 (100%)	0	0	11
0.5	10 (100%)	0	0	0	10 (100%)	0	0	10
>32	1 (100%)	0	0	0	1 (100%)	0	0	1
Total	21	0	1	0	22	0	0	22

ITT=Intent-to-Treat; PPb=Per-Protocol clinical and bacteriological; MIC=minimum inhibitory concentration; Erad=eradication; Persist=persistence; Col=colonization; Indeter=indeterminate

Presumed eradication was collapsed with eradication. Presumed persistence was collapsed with persistence.

a Pretreatment MIC assessment was made on or before Day 1.

Table 38: Pretreatment MIC Distributions for *M. catarrhalis* Versus Bacteriological and Clinical Responses for Cethromycin and Clarithromycin (ITT and PPb Populations: Studies CL05-001 and CL06-001 Combined)

MIC[a] (μg/mL)	Bacteriological Response			Clinical Response			Total
	Erad	Persist	Indeter	Cure	Failure	Indeter	
ITT Population							
Cethromycin 300 mg QD							
0.06	3 (100%)	0	0	3 (100%)	0	0	3
0.12	1 (50.0%)	0	1 (50.0%)	1 (50.0%)	0	1 (50.0%)	2
0.25	1 (50.0%)	1 (50.0%)	0	1 (50.0%)	1 (50.0%)	0	2
Total	5	1	1	5	1	1	7
Clarithromycin 250 mg BID							
0.12	7 (100%)	0	0	7 (100%)	0	0	7
0.25	3 (100%)	0	0	2 (66.7%)	1 (33.3%)	0	3
Total	10	0	0	9	1	0	10
PPb Population							
Cethromycin 300 mg QD							
0.06	2 (100%)	0	0	2 (100%)	0	0	2
0.12	1 (100%)	0	0	1 (100%)	0	0	1
0.25	1 (50.0%)	1 (50.0%)	0	1 (50.0%)	1 (50.0%)	0	2
Total	4	1	0	4	1	0	5
Clarithromycin 250 mg BID							
0.12	7 (100%)	0	0	7 (100%)	0	0	7
0.25	3 (100%)	0	0	2 (66.7%)	1 (33.3%)	0	3
Total	10	0	0	9	1	0	10

ITT=Intent-to-Treat; PPb=Per-Protocol clinical and bacteriological; MIC=minimum inhibitory concentration; Erad=eradication; Persist=persistence; Indeter=indeterminate

Presumed eradication was collapsed with eradication. Presumed persistence was collapsed with persistence.

a Pretreatment MIC assessment was made on or before Day 1.

Pretreatment oxacillin susceptibility of *S. aureus* (<4 μg/mL) versus bacteriological and clinical responses for cethromycin and clarithromycin for the ITT population for the integrated analysis are summarized in Table 39. There was 1 subject in the cethromycin group and 1 subject in the clarithromycin group with oxacillin-resistant *S. aureus* in the ITT population. Both subjects achieved clinical cure and bacteriological eradication/presumed eradication.

Table 39: Pretreatment Oxacillin Susceptibility of *S. aureus* Versus Bacteriological and Clinical Responses for Cethromycin and Clarithromycin (ITT Population: Studies CL05-001 and CL06-001 Combined)

MIC[a] (μg/mL)	Bacteriological Response				Clinical Response			Total
	Erad	Persist	Col	Indeter	Cure	Failure	Indeter	
Cethromycin 300 mg QD								
0.25	7 (53.8%)	2 (15.4%)	1 (7.7%)	3 (23.1%)	8 (61.5%)	2 (15.4%)	3 (23.1%)	13
0.5	6 (100%)	0	0	0	6 (100%)	0	0	6
1	2 (100%)	0	0	0	2 (100%)	0	0	2
>4	1 (100%)	0	0	0	1 (100%)	0	0	1
Total	16	2	1	3	17	2	3	22
Clarithromycin 250 mg BID								
≤0.12	1 (50.0%)	0	0	1 (50.0%)	1 (50.0%)	0	1 (50.0%)	2
0.25	12 (85.7%)	0	1 (7.1%)	1 (7.1%)	13 (92.9%)	0	1 (7.1%)	14
0.5	5 (83.3%)	0	0	1 (16.7%)	5 (83.3%)	0	1 (16.7%)	6
1	2 (100%)	0	0	0	2 (100%)	0	0	2
4	1 (100%)	0	0	0	1 (100%)	0	0	1
Total	21	0	1	3	22	0	3	25

ITT=Intent-to-Treat; MIC=minimum inhibitory concentration; Erad=eradication; Persist=persistence; Indeter=indeterminate

Presumed eradication was collapsed with eradication. Presumed persistence was collapsed with persistence.

a Pretreatment MIC assessment was made on or before Day 1.

Pretreatment penicillin susceptibility of *S. pneumoniae* (<8 μg/mL) versus bacteriological and clinical responses for cethromycin and clarithromycin for the ITT population for the integrated analyses are summarized in Table 40. No subject had PRSP in the ITT population.

Table 40: Pretreatment Penicillin Susceptibility of *S. pneumoniae* Versus Bacteriological and Clinical Responses for Cethromycin and Clarithromycin (ITT Population: Studies CL05-001 and CL06-001 Combined)

MIC[a] (μg/mL)	Bacteriological Response			Clinical Response			Total
	Erad	Persist	Indeter	Cure	Failure	Indeter	
Cethromycin 300 mg QD							
≤0.008	1 (50.0%)	0	1 (50.0%)	1 (50.0%)	0	1 (50.0%)	2
0.015	11 (78.6%)	2 (14.3%)	1 (7.1%)	11 (78.6%)	2 (14.3%)	1 (7.1%)	14
0.03	7 (87.5%)	0	1 (12.5%)	6 (75.0%)	0	2 (25.0%)	8
0.06	1 (100%)	0	0	1 (100%)	0	0	1
0.25	1 (100%)	0	0	1 (100%)	0	0	1
0.5	2 (100%)	0	0	2 (100%)	0	0	2
1	2 (100%)	0	0	2 (100%)	0	0	2
2	1 (100%)	0	0	1 (100%)	0	0	1
Total	26	2	3	25	2	4	31
Clarithromycin 250 mg BID							
≤0.008	1 (100%)	0	0	1 (100%)	0	0	1
0.015	11 (84.6%)	1 (7.7%)	1 (7.7%)	11 (84.6%)	1 (7.7%)	1 (7.7%)	13
0.03	3 (75.0%)	1 (25.0%)	0	1 (25.0%)	2 (50.0%)	1 (25.0%)	4
0.06	2 (100%)	0	0	2 (100%)	0	0	2
0.12	3 (100%)	0	0	2 (66.7%)	1 (33.3%)	0	3
0.5	1 (100%)	0	0	1 (100%)	0	0	1
1	3 (75.0%)	0	1 (25.0%)	2 (50.0%)	1 (25.0%)	1 (25.0%)	4
2	2 (100%)	0	0	2 (100%)	0	0	2
Missing	2 (66.7%)	0	1 (33.3%)	2 (66.7%)	0	1 (33.3%)	3
Total	28	2	3	24	5	4	33

ITT=Intent-to-Treat; MIC=minimum inhibitory concentration; Erad=eradication; Persist=persistence; Indeter=indeterminate

Missing=susceptibility test was not performed.

Presumed eradication was collapsed with eradication. Presumed persistence was collapsed with persistence.

a Pretreatment MIC assessment was made on or before Day 1.

Pretreatment erythromycin susceptibility of *S. pneumoniae* (<1 μg/mL) versus bacteriological and clinical responses for cethromycin and clarithromycin for the ITT population for the integrated analyses are summarized in Table 41. There were 5 subjects in the cethromycin group and 6 subjects in the clarithromycin group with erythromycin-resistant *S. pneumoniae.* All of these subjects achieved clinical cure and bacteriological eradication/presumed eradication, except for 2 subjects (1 cethromycin and 1 clarithromycin) who had an indeterminate outcome for both clinical and bacteriological response.

Table 41: Pretreatment Erythromycin Susceptibility of *S. pneumoniae* Versus Bacteriological and Clinical Responses for Cethromycin and Clarithromycin (ITT Population: Studies CL05-001 and CL06-001 Combined)

MIC[a] (μg/mL)	Bacteriological Response			Clinical Response			Total
	Erad	Persist	Indeter	Cure	Failure	Indeter	
Cethromycin 300 mg QD							
0.03	1 (50.0%)	0	1 (50.0%)	1 (50.0%)	0	1 (50.0%)	2
0.06	19 (90.5%)	2 (9.5%)	0	18 (85.7%)	2 (9.5%)	1 (4.8%)	21
0.12	2 (66.7%)	0	1 (33.3%)	2 (66.7%)	0	1 (33.3%)	3
4	2 (100%)	0	0	2 (100%)	0	0	2
8	1 (100%)	0	0	1 (100%)	0	0	1
16	0	0	1 (100%)	0	0	1 (100%)	1
>16	1 (100%)	0	0	1 (100%)	0	0	1
Total	26	2	3	25	2	4	31
Clarithromycin 250 mg BID							
0.015	1 (100%)	0	0	1 (100%)	0	0	1
0.03	3 (100%)	0	0	2 (66.7%)	1 (33.3%)	0	3
0.06	13 (86.7%)	1 (6.7%)	1 (6.7%)	12 (80.0%)	2 (13.3%)	1 (6.7%)	15
0.12	3 (75.0%)	1 (25.0%)	0	1 (25.0%)	2 (50.0%)	1 (25.0%)	4
0.25	1 (100%)	0	0	1 (100%)	0	0	1
4	2 (100%)	0	0	2 (100%)	0	0	2
16	1 (100%)	0	0	1 (100%)	0	0	1
>16	2 (66.7%)	0	1 (33.3%)	2 (66.7%)	0	1 (33.3%)	3
Missing	2 (66.7%)	0	1 (33.3%)	2 (66.7%)	0	1 (33.3%)	3
Total	28	2	3	24	5	4	33

ITT=Intent-to-Treat; MIC=minimum inhibitory concentration; Erad=eradication; Persist=persistence; Indeter=indeterminate

Missing=susceptibility test was not performed.

Presumed eradication was collapsed with eradication. Presumed persistence was collapsed with persistence.

a Pretreatment MIC assessment was made on or before Day 1.

Subjects with pathogen isolates showing a 4-fold increase in MIC or a 3 mm decrease in zone diameter pretreatment to post-treatment were identified. One subject in the clarithromycin group with *S. aureus* had an increase in MIC from 0.25 μg/mL to >32 μg/mL and a decrease in zone diameter from 29 mm to 6 mm from Visit 1 to Visit 4. The subject achieved clinical cure with bacteriological response of colonization. No other subjects demonstrated a 4-fold increase in MIC or a 3 mm decrease in zone diameter from pretreatment to post-treatment.

7.1.5 Results for Subpopulations

7.1.5.1. Subpopulations Defined by Demographics, Drugs, and Diseases

Analyses of potential drug-demographic interactions were limited to the Phase III controlled CAP studies. Clinical and bacteriological cure rates were summarized by gender, race (White vs. Non-white), age (<65 vs. ≥65), country (US vs. Non-US), tobacco use (user vs. former/never), and Fine criteria (I vs. II, III, and IV). The treatment-by-subgroup interaction was assessed in the ITT and PPc populations. Absence of a treatment-by-subgroup interaction indicates that treatment differences are consistent among subgroups.

No statistically significant or clinically important treatment-by-subgroup interactions were observed. Thus, the differences between cethromycin- and clarithromycin-treated subjects were consistent among subgroups of subjects defined by gender, race, age, country, tobacco use, and Fine criteria.

In the Phase III clinical program, subjects receiving concomitant medications believed to interact with the CYP3A system were excluded. As a result, no meaningful drug-drug interaction analysis was able to be performed.

Clinical cure rates were summarized by subjects with a history of cardiac disease, hepatic disease, and diabetes. The treatment-by-subgroup interaction was assessed in the ITT population. No statistically significant or clinically important treatment-by-subgroup interactions were observed. Thus, the differences between cethromycin- and clarithromycin-treated subjects were consistent among subgroups of subjects defined by history of cardiac disease, hepatic disease, and diabetes.

7.1.5.2. Subpopulations Defined by Erythromycin Susceptibility and Pneumococcal Bacteremia

Clinical and bacteriological outcomes are presented for subjects with *S. pneumoniae* by pretreatment erythromycin susceptibility. In addition, clinical and bacteriological outcomes are presented for subjects with pneumococcal bacteremia. These presentations include data from the 2 Phase III controlled CAP studies conducted by Advanced Life Sciences (Studies CL05-001 and CL06-001) and the 2 uncontrolled CAP studies conducted by Abbott Laboratories (Studies M99-054 and M00-219) as part of the cethromycin clinical program.

Subjects with *S. pneumoniae* by Pretreatment Erythromycin Susceptibility

Among cethromycin-treated subjects in the ITT population in the 2 controlled and 2 uncontrolled CAP studies, a total of 143 *S. pneumoniae* isolates (112 from the uncontrolled studies and 31 from the controlled studies) had results of pretreatment erythromycin susceptibility testing. Of these, 17 isolates (12 from the uncontrolled studies and 5 from the controlled studies) were resistant to erythromycin (MIC ≥1 μg/mL).

Among clarithromycin-treated subjects in the ITT population in the 2 controlled CAP studies, a total of 30 *S. pneumoniae* isolates had results of pretreatment erythromycin susceptibility testing. Of these, 6 isolates were resistant to erythromycin (MIC ≥1 μg/mL). A summary of the clinical and bacteriological responses by pretreatment erythromycin susceptibility for *S. pneumoniae* isolates in the 2 controlled and 2 uncontrolled CAP studies is presented in Table 42.

Table 42: Clinical and Bacteriological Outcomes by Pretreatment Erythromycin Susceptibility for *S. pneumoniae* Isolates in the Controlled and Uncontrolled CAP Studies (ITT Population)

Study	Dose	Susceptibility[a]	Clinical Response			Bacteriological Response		
			Cure	Failure	Indeterminate	Presumed Eradication	Presumed Persistence	Indeterminate
M99-054	Cethromycin 300 mg QD	Susceptible	11 (78.6%)	2 (14.3%)	1 (7.1%)	11 (78.6%)	2 (14.3%)	1 (7.1%)
		Intermediate	0	0	0	0	0	0
		Resistant	1 (100%)	0	0	1 (100%)	0	0
	Cethromycin 600 mg QD	Susceptible	5 (83.3%)	0	1 (16.7%)	5 (83.3%)	0	1 (16.7%)
		Intermediate	0	0	0	0	0	0
		Resistant	1 (100%)	0	0	1 (100%)	0	0
M00-219	Cethromycin 150 mg QD	Susceptible	29 (82.9%)	0	6 (17.1%)	29 (82.9%)	0	6 (17.1%)
		Intermediate	0	0	0	0	0	0
		Resistant	4 (100%)	0	0	4 (100%)	0	0
	Cethromycin 150 mg BID	Susceptible	39 (88.6%)	2 (4.5%)	3 (6.8%)	40 (90.9%)	1 (2.3%)	3 (6.8%)
		Intermediate	1 (100%)	0	0	1 (100%)	0	0
		Resistant	5 (83.3%)	1 (16.6%)	0	5 (83.3%)	1 (16.6%)	0
CL05-001	Cethromycin 300 mg QD	Susceptible	8 (80.0%)	0	2 (20.0%)	8 (80.0%)	0	2 (20.0%)
		Intermediate	0	0	0	0	0	0
		Resistant	2 (100%)	0	0	2 (100%)	0	0
	Clarithromycin 250 mg BID	Susceptible	12 (75.0%)	3 (18.8%)	1 (6.3%)	15 (93.8%)	1 (6.3%)	0
		Intermediate	0	0	0	0	0	0
		Resistant	5 (83.3%)	0	1 (16.7%)	5 (83.3%)	0	1 (16.7%)
CL06-001	Cethromycin 300 mg QD	Susceptible	13 (81.3%)	2 (12.5%)	1 (6.3%)	14 (87.5%)	2 (12.5%)	0
		Intermediate	0	0	0	0	0	0
		Resistant	2 (66.6%)	0	1 (33.3%)	2 (66.6%)	0	1 (33.3%)
	Clarithromycin 250 mg BID	Susceptible	5 (62.5%)	2 (25.0%)	1 (12.5%)	6 (75.0%)	1 (12.5%)	1 (12.5%)
		Intermediate	0	0	0	0	0	0
		Resistant	0	0	0	0	0	0

ITT=Intent-to-Treat

a Erythromycin breakpoints for *S. pneumoniae*; susceptible MIC ≤0.25 µg/mL, intermediate MIC >0.25 but <1 µg/mL, resistant MIC ≥1 µg/mL.

Among cethromycin-treated subjects in the ITT population in the 2 controlled and 2 uncontrolled CAP studies combined who had *S. pneumoniae* isolated, the clinical cure rates were 84.0% (105/125) for erythromycin-susceptible isolates and 88.2% (15/17) for erythromycin-resistant isolates. Similarly, the bacteriological eradication rates were 85.6% (107/125) for erythromycin-susceptible isolates and 88.2% (15/17) for erythromycin-resistant isolates.

Among cethromycin-treated subjects in the ITT population in the 2 controlled CAP studies combined who had *S. pneumoniae* isolated, the clinical cure rates were 80.8% (21/26) for erythromycin-susceptible isolates and 80.0% (4/5) for erythromycin-resistant isolates. Among clarithromycin-treated subjects in the ITT population in the 2 controlled CAP studies combined who had *S. pneumoniae* isolated, the clinical cure rates were 70.8% (17/24) for erythromycin-susceptible isolates and 83.3% (5/6) for erythromycin-resistant isolates. The bacteriological eradication rates were 84.6% (22/26) for erythromycin-susceptible isolates and 80.0% (4/5) for erythromycin-resistant isolates among cethromycin-treated subjects and 87.5% (21/24) for erythromycin-susceptible isolates and 83.3% (5/6) for erythromycin-resistant isolates among clarithromycin-treated subjects. A summary of clinical cure rates and bacteriological eradication rates for subjects with *S. pneumoniae* by pretreatment erythromycin susceptibility in the 2 controlled and 2 uncontrolled CAP studies is presented in Table 43.

Table 43: Clinical Cure Rates and Bacteriological Eradication Rates by Pretreatment Erythromycin Susceptibility for *S. pneumoniae* Isolates in the Controlled and Uncontrolled CAP Studies (ITT Population)

	Clinical Cure Rate		Bacteriological Eradication Rate	
	Erythromycin-Susceptible *S. pneumoniae*	Erythromycin-Resistant *S. pneumoniae*	Erythromycin-Susceptible *S. pneumoniae*	Erythromycin-Resistant *S. pneumoniae*
All CAP Studies (Controlled and Uncontrolled)				
Cethromycin All Doses	84.0% (105/125)	88.2% (15/17)	85.6% (107/125)	88.2% (15/17)
Controlled CAP Studies				
Cethromycin 300 mg QD	80.8% (21/26)	80.0% (4/5)	84.6% (22/26)	80.0% (4/5)
Clarithromycin 250 mg BID	70.8% (17/24)	83.3% (5/6)	87.5% (21/24)	83.3% (5/6)

ITT=Intent-to-Treat

Subjects with *S. pneumoniae* Bacteremia

Among cethromycin-treated subjects in the ITT population in the 2 controlled and 2 uncontrolled CAP studies, a total of 9 (4 from the uncontrolled studies and 5 from the controlled studies) had pneumococcal bacteremia. Of these 9 subjects, 7 (77.8%) were classified as clinical cures; the remaining 2 subjects were terminated early from the study and had indeterminate clinical responses. Eight of the 9 (88.9%) bacteremic subjects had bacteriological responses of eradication or presumed eradication. The remaining subject was terminated from the study following 1 day of cethromycin therapy due to a false-positive pregnancy test and had an

indeterminate bacteriological response. The subject was noted as a clinical cure at the follow-up visit.

In the ITT population of the 2 controlled CAP studies, a total of 5 subjects in the cethromycin group and 5 subjects in the clarithromycin group had pneumococcal bacteremia. Clinical cure was observed in 3 of the 5 subjects (60.0%) in the cethromycin group and in 1 of the 5 subjects (20.0%) in the clarithromycin group. Four of the 5 subjects in each treatment group (80.0%) had bacteriological responses of eradication or presumed eradication. The cethromycin subject that had an indeterminate bacteriological response was previously discussed. The clarithromycin subject that had an indeterminate bacteriological response died during treatment.

All *S. pneumoniae* isolates from these bacteremic subjects were susceptible to both erythromycin and penicillin, with the exception of the isolate from the clarithromycin subject discussed above who died during treatment. This subject was infected with an erythromycin-resistant, PSSP.

A summary of clinical and bacteriological outcomes for the subgroup of subjects with *S. pneumoniae* bacteremia in the 2 controlled and 2 uncontrolled CAP studies is presented in Table 44.

Table 44: Clinical and Bacteriological Outcomes for the Subgroup of Subjects with *S. pneumoniae* Bacteremia in the Controlled and Uncontrolled CAP Studies (ITT Population)

Subject Number	Fine Criteria Classification	*S. pneumoniae* Susceptibility	Clinical Response	Bacteriological Response
Uncontrolled CAP Studies – Subjects receiving cethromycin				
30494-16384	Not Collected	ery S, pen S	Cure	Presumed Eradication
30829-15101	Not Collected	ery S, pen S	Cure	Presumed Eradication
30845-12356	Not Collected	ery S, pen S	Cure	Presumed Eradication
30881-15014	Not Collected	ery S, pen S	Cure	Presumed Eradication
Controlled CAP Studies – Subjects receiving cethromycin				
1074-0008	FINE I	ery S, pen S	Indeterminate	Indeterminate
1085-0001	FINE II	ery S, pen S	Cure	Presumed Eradication
3013-0026	FINE IV	ery S, pen S	Cure	Eradication
4118-0004	FINE IV	ery S, pen S	Indeterminate	Eradication
5101-0004	FINE III	ery S, pen S	Cure	Eradication
Controlled CAP Studies – Subjects receiving clarithromycin				
1082-0012	FINE II	ery S, pen S	Indeterminate	Eradication
3004-0013	FINE II	ery R, pen S	Indeterminate	Indeterminate
3013-0028	FINE II	ery S, pen S	Cure	Eradication
3023-0004	FINE I	ery S, pen S	Failure	Eradication
3025-0004	FINE II	ery S, pen S	Failure	Eradication

ITT=Intent-to-Treat; ery=erythromycin; pen=penicillin; S=susceptible; R=resistant

7.2. Supportive Efficacy Studies

Two double-blind, randomized studies conducted by Abbott Laboratories included a 300 mg/day dose of cethromycin.

- Study M99-054 was a Phase II, double-blind, randomized, parallel-group, multicenter study in subjects with a clinical diagnosis of CAP that was confirmed by a positive chest x-ray and supported by appropriate signs and symptoms. Subjects were randomly assigned in a 1:1 ratio at each investigational site to receive either cethromycin 300 mg QD or 600 mg QD for 7 days.
- Study M00-219 was a Phase II/III, double-blind, randomized, parallel-group, multicenter study in subjects with a clinical diagnosis of CAP that was confirmed by a positive chest x-ray and supported by appropriate signs and symptoms. Subjects were randomly assigned in a 1:1 ratio at each investigational site to receive either cethromycin 150 mg QD or 150 mg BID for 10 days.

In Study M99-054, 187 subjects (300 mg QD: 95; 600 mg QD: 92) were randomized and dosed. No clinically important differences were noted between the dose groups for demographic characteristics or pretreatment signs and symptoms. The proportion of subjects who completed study drug treatment was higher in the cethromycin 300 mg QD group (91%) compared with the 600 mg QD group (83%). Among ITT subjects, clinical cure rates were 84% in the cethromycin 300 mg QD group and 73% in the cethromycin 600 mg QD group.

In Study M00-219, a total of 583 subjects (150 mg QD: 284; 150 mg BID: 299) were randomized and dosed. No clinically important differences were noted between the dose groups for demographic characteristics or pretreatment signs and symptoms. The proportions of subjects who completed the study drug treatment were similar between the dose groups (88% in each dose group). Among ITT subjects, clinical cure rates were 83% in the cethromycin 150 mg QD group and 81% in the cethromycin 150 mg BID group.

Overall, these 2 studies provide supportive evidence of the efficacy of cethromycin when dosed at 300 mg/day. The 300 mg QD dose had a higher clinical cure rate than the 150 mg BID dose (91% versus 81%).

7.3. Dose Response

The antibacterial effect of many antibiotics on target organisms has been empirically found to correlate with C_{max}, AUC, or the fraction of time that antibiotic concentrations are above a threshold (e.g., MIC_{90}).

Results from *in vitro* studies provided estimates of the cethromycin MIC_{90} for the following target respiratory organisms:

- *S. pneumoniae*: ≤0.125 μg/mL or 125 ng/mL against penicillin-susceptible, penicillin-intermediate, or penicillin-resistant isolates
- *H. influenzae*: 4 μg/mL or 4000 ng/mL, regardless of β-lactamase production
- *S. aureus*: 0.03-0.125 μg/mL or 30-125 ng/mL against methicillin-susceptible isolates

- *M. catarrhalis*: 0.06-0.12 μg/mL or 60-120 ng/mL, regardless of β-lactamase production
- *C. pneumoniae*: 0.015 μg/mL or 150 ng/mL
- *L. pneumophila*: 0.03-0.06 μg/mL or 30-150 ng/mL
- *M. pneumoniae*: ≤0.001 μg/mL or 1 ng/mL

Results following 5 days of QD dosing from Study CL07-001(see Section 8.10.1) indicated that a cethromycin dose of 300 mg provides peak plasma concentrations of cethromycin sufficient to exceed the MIC_{90} of all target pathogens, except *H. influenzae* (Table 45).

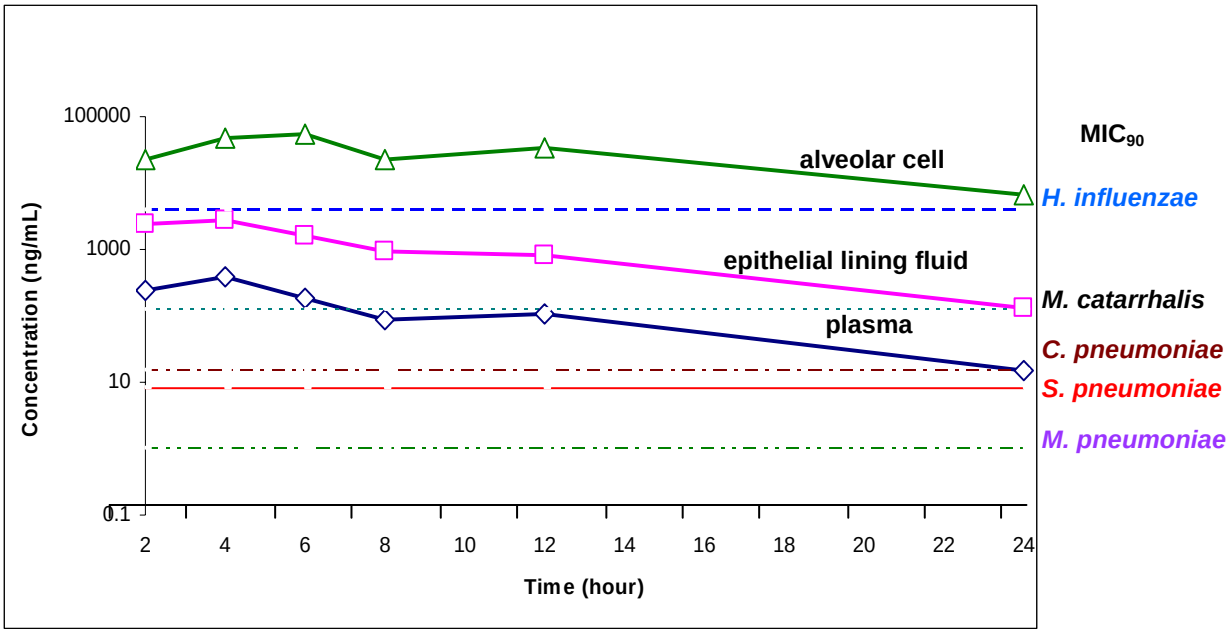
Table 45: Mean Plasma Pharmacokinetic Parameters of Cethromycin Following 5 Days of 300 mg QD Dosing (Study CL07-001)

Dose (mg) Fasting	N	C_{max} (ng/mL)	AUC (ng·h/mL)
300 mg QD	59	686.15	5236.81

C_{max}=maximum concentration; AUC=area under the curve

However, compared to plasma, cethromycin concentrations are 7- to 9-fold higher in the extracellular lavage fluid (ELF) and 35- to 235-fold higher in the AC when dosed at 150 mg QD for 5 days (Study M00-262). These ratios were similar to what had been observed in a similar study (Study M99-142) that used a dosing schedule of 300 mg QD for 5 days. In that study, the mean peak concentration in ELF was 5.5-fold that of plasma and the mean AUC was 8-fold that of plasma, while mean peak concentration in AC was 11-fold that of plasma and mean AUC was 210-fold that of plasma.

Figure 7: Pulmonary Tissue Concentration Profile (Cethromycin 300 mg QD for 5 Days)



The accumulation of cethromycin in lung tissues is expected to produce higher intrapulmonary C_{max} to MIC_{90} (C_{max}/MIC) and AUC to MIC_{90} (AUC/MIC) ratios and a prolonged percentage of time above the MIC_{90} (%T>MIC), supporting QD dosing for the treatment of respiratory infections. Based on the ratios determined from animal models, cethromycin dosed at 300 mg QD for 5 days exceeded the predicted values for 3 of the 5 groups of pathogens in plasma, 4 of the 5 groups in ELF, and all 5 groups in AC (Table 46).

Table 46: Summary of Pharmacokinetic/Pharmacodynamic Relationships Observed in Healthy Subjects Treated with Cethromycin 300 mg Once Daily

Organism (MIC_{90}, µg/mL)	Plasma[a]			ELF[a]			AC[a]		
	C_{max}/ MIC	AUC/ MIC	%T> MIC	C_{max}/ MIC	AUC/ MIC	%T> MIC	C_{max}/ MIC	AUC/ MIC	%T> MIC
S. pneumoniae (0.008)	63	383	100	344	3,224	100	6,925	90,050	100
H. influenzae (4)	0.13	0.77	0	0.69	6	0	14	159	100
M. catarrhalis (0.12)	4	25	39	23	215	100	462	6,083	100
C. pneumoniae (0.015)	33	204	100	183	1,800	100	3,693	50,693	100
M. pneumoniae[b] (≤0.001)	504	3,064	100	2,752	25,792	100	55,400	760,400	100

ELF=extracellular lavage fluid; AC=alveolar cells; MIC_{90}=concentration at which 90% of target organisms are killed.

a Pharmacokinetic parameters were calculated based on the total cethromycin concentrations including protein-bound and unbound fractions.

b MIC_{90} of 0.001 µg/mL was used for the pharmacodynamic calculations.

An increase in overall clinical cure rate from daily doses of 150 mg to 600 mg was not observed in the dose-ranging studies. As suggested by *in vitro* results, the clinical cure rate for *H. influenzae* did increase from 150 mg QD to 300 mg QD (Table 47). Comparisons across daily dose groups must be made cautiously because the 150 mg QD and 150 mg BID groups were dosed for 10 days and the 300 mg QD and 600 mg QD groups were dosed for 7 days.

Table 47: Clinical Cure Rates Overall and for Selected Organisms (ITT and PPb Populations: Studies M99-054 and M00-219)

Organism	Population	Cethromycin Regimen			
		150 mg QD[a]	150 mg BID[a]	300 mg QD[b]	600 mg QD[b]
Overall	ITT[c]	218/264 (83%)	222/274 (81%)	80/95 (84%)	65/89 (73%)
	PPb	138/144 (96%)	125/145 (86%)	54/59 (92%)	46/56 (82%)
S. pneumoniae	ITT[c]	33/40 (83%)	49/56 (88%)	14/17 (82%)	6/7 (86%)
	PPb	33/33 (100%)	49/53 (92%)	13/15 (87%)	6/6 (100%)
H. influenzae	ITT[c]	35/43 (81%)	32/44 (73%)	9/9 (100%)	15/23 (65%)
	PPb	34/36 (94%)	32/42 (76%)	9/9 (100%)	13/18 (72%)
M. catarrhalis	ITT[c]	12/13 (92%)	9/11 (82%)	6/9 (67%)	2/5 (40%)
	PPb	12/13 (92%)	9/10 (90%)	6/8 (75%)	2/4 (50%)
C. pneumoniae	ITT[c]	15/15 (100%)	8/11 (73%)	21/25 (84%)	22/30 (73%)
	PPb	15/15 (100%)	7/8 (88%)	19/20 (95%)	19/24 (79%)
M. pneumoniae	ITT[c]	19/19 (100%)	13/16 (81%)	14/15 (93%)	15/19 (79%)
	PPb	19/19 (100%)	12/13 (92%)	13/14 (93%)	14/15 (93%)

ITT=Intent-to-Treat; PPb=Per-Protocol clinical and bacteriological
a Dosed 10 days (Study M00-219)
b Dosed 7 days (Study M99-054)
c Subjects with 'indeterminate' or 'missing/not done' outcomes were treated as clinical failures in the analyses of the ITT population.

7.4. Efficacy Conclusions

The efficacy of cethromycin 300 mg QD dosed for 7 days was confirmed in the 2 active-controlled, double-blind, randomized, parallel-group CAP studies CL05-001 and CL06-001 (Table 28). In summary:

- Cethromycin 300 mg QD demonstrated non-inferiority to clarithromycin 250 mg BID in the primary endpoint of clinical cure rate for the treatment of CAP.
- Bacteriological cure rates, pathogen eradication rates, and radiological success rates were similar for cethromycin and clarithromycin.
- Clinical cure correlated with bacteriological eradication of target pathogens in both treatment groups.

Thus, the clinical development program has demonstrated that oral cethromycin is effective for the treatment of mild to moderate CAP in patients 18 years of age and above.

8. SAFETY

The overall clinical program supporting the use of cethromycin for the treatment of CAP includes data from a total of 49 studies. Of these, 37 were Phase I trials and 12 were Phase II/III trials. The clinical program included 46 studies conducted by Abbott Laboratories and 3 studies conducted by Advanced Life Sciences (one Phase I safety study and two Phase III controlled efficacy and safety studies).

Throughout this document, tabular presentations of safety data are limited to the following groups: all cethromycin doses; cethromycin 300 mg QD; cethromycin 300 mg TDD; cethromycin ≥300 QD; as well as placebo and active controls, where applicable. Descriptive information from groups that included cethromycin TDD of <300 mg and >300 mg are presented in the document where appropriate for analysis of dose-response. Other than in the overall disposition of subjects, only those subjects included in the safety population are summarized.

8.1. Exposure to the Drug

A total of 5095 subjects received at least one dose of cethromycin in the Phase I, II, and III studies that were integrated across the cethromycin clinical program. Of these, 6 subjects had no post-baseline assessments and were excluded from the safety population. Thus, 5089 subjects received at least one dose of cethromycin in the Phase I, II, and III studies, had at least one post-baseline safety assessment, and have been included in the safety population for analysis.

Of all cethromycin-treated subjects in the Phase I, II, and III studies combined included in the safety population, 2195 received a TDD of 300 mg, administered as either 100 mg three times daily (TID), 150 mg BID, or 300 mg QD. A total of 1375 subjects received cethromycin 300 mg QD, the dose for which approval is sought, and 1863 received cethromycin ≥300 mg QD, which included doses of 300 mg QD, 600 mg QD, 800 mg QD, 900 mg QD, and 1200 mg QD. In addition, 230 subjects received placebo in the Phase I studies and 1721 subjects received active controls in the Phase I, II, and III studies that included clarithromycin, moxifloxacin, azithromycin, levofloxacin, and penicillin V.

Total daily doses of cethromycin <300 mg were received by 2219 subjects and >300 mg were received by 757 subjects.

Among all cethromycin-treated subjects in the Phase I, II, and III studies combined, total drug exposure ranged from 100 mg to 10800 mg, with a mean total dose of 1927.9 mg. Treatment duration was ≥6 days for 63.6% of all cethromycin-treated subjects. Drug exposure was similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

Among subjects who received cethromycin 300 mg QD in the Phase I, II, and III studies combined, total drug exposure ranged from 300 mg to 4500 mg, with a mean total dose of 1901.2 mg. Treatment duration was ≥6 days for 63.2% of subjects who received cethromycin 300 mg QD. A summary of cethromycin exposure in all Phase I, II, and III studies combined is presented for selected treatment groups in Table 48.

Table 48: Cethromycin Exposure for Selected Treatment Groups (All Phase I, II, and III Studies)

	Cethromycin			
	300 mg TDD (N=2195)	**300 mg QD (N=1375)**	**≥300 mg QD (N=1863)**	**All Doses (N=5089)**
Total Cethromycin Dose (mg)				
Mean (SD)	2148.2 (907.05)	1901.2 (666.80)	2330.7 (1216.96)	1927.9 (1282.54)
Median	2100.0	2100.0	2100.0	1500.0
Minimum, Maximum	300, 4500	300, 4500	300, 6000	100, 10800
Duration of Treatment (Days)				
1	142 (6.5)	55 (4.0)	93 (5.0)	306 (6.0)
2-5	530 (24.1)	451 (32.8)	713 (38.3)	1544 (30.3)
6-7	658 (30.0)	582 (42.3)	686 (36.8)	1055 (20.7)
>7	865 (39.4)	287 (20.9)	371 (19.9)	2184 (42.9)

mg=milligrams; TDD=total daily dose; QD=once daily; SD=standard deviation
Note: Percentages are displayed in parentheses, except where noted as SD.

8.2. Disposition

Among all cethromycin-treated subjects in the Phase I, II, and III studies combined, the majority completed study participation (89.3%). The most common reasons for discontinuation from study were adverse event (3.2%), clinical failure (2.2%), withdrawal of consent (1.1%), and other (3.2%). Each of the remaining reasons that led to discontinuation from study were reported by <1% of the subjects. Subject disposition was similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

Among subjects who received cethromycin 300 mg QD in the Phase I, II, and III studies combined, the majority completed study participation (92.9%). The most common reasons for discontinuation from study were adverse event (2.3%), clinical failure (1.2%), and other (1.2%). Each of the remaining reasons that led to discontinuation from study were reported by <1% of the subjects. A summary of disposition of subjects in all Phase I, II, and III studies combined is presented for selected treatment groups in Table 49.

Table 49: Disposition of Subjects for Selected Treatment Groups (All Phase I, II, and III Studies)

	Placebo	Cethromycin				
		300 mg TDD	300 mg QD	≥300 mg QD	All Doses	Active Controls
Number Treated	230	2199	1379	1867	5095	1724
Reasons for Ineligibility from Safety Analysis						
Lost to Follow-Up	0	3 (0.1)	3 (0.2)	3 (0.2)	5 (0.1)	0
Withdrew Consent	0	1 (0.0)	1 (0.1)	1 (0.1)	1 (0.0)	3 (0.2)
Number Eligible for Safety Analysis	230 (100)	2195 (99.8)	1375 (99.7)	1863 (99.8)	5089 (99.9)	1721 (99.8)
Number Completed Study	217 (94.3)	2006 (91.4)	1278 (92.9)	1706 (91.6)	4547 (89.3)	1557 (90.5)
Reasons for Discontinuation[a]						
Adverse Event	1 (0.4)	51 (2.3)	32 (2.3)	59 (3.2)	162 (3.2)	62 (3.6)
Clinical Failure	0	39 (1.8)	16 (1.2)	16 (0.9)	114 (2.2)	46 (2.7)
Lost To Follow-Up	0	16 (0.7)	6 (0.4)	8 (0.4)	46 (0.9)	21 (1.2)
Principal Investigator Decision	0	5 (0.2)	5 (0.4)	15 (0.8)	17 (0.3)	0
Selection Criteria Were Violated After Enrollment	0	3 (0.1)	3 (0.2)	5 (0.3)	5 (0.1)	0
Significant Alteration In Lab Value	0	1 (0.0)	1 (0.1)	1 (0.1)	1 (0.0)	0
Subject Did Not Meet Entrance Criteria	0	7 (0.3)	6 (0.4)	9 (0.5)	13 (0.3)	0
Subject Noncompliance	0	1 (0.0)	1 (0.1)	1 (0.1)	1 (0.0)	0
Withdrew Consent	0	21 (1.0)	10 (0.7)	17 (0.9)	54 (1.1)	12 (0.7)
Other	12 (5.2)	53 (2.4)	17 (1.2)	26 (1.4)	162 (3.2)	38 (2.2)

mg=milligrams; TDD=total daily dose; QD=once daily
Note: Percentages are displayed in parentheses.
a Subjects may have had more than 1 reason for discontinuation.

8.3. Demographic and Selected Baseline Characteristics

8.3.1 All Phase I Studies Combined

Among all cethromycin-treated subjects in the Phase I studies combined, age ranged from 18 to 76 years, with a mean age of 32.8 years. The majority of the subjects were male (74.9%), White (83.1%), and from the USA (70.6%). Most had never used or were former users of tobacco and alcohol. The percentage of subjects who reported current use of alcohol was higher in the all cethromycin-treated subjects group compared with the placebo group. The active control group had a lower mean age and greater proportions of subjects who were White, from outside the US, and current users of tobacco compared with the all cethromycin-treated subjects group. Subject demographic and baseline characteristics were similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

Among subjects who received cethromycin 300 mg QD in the Phase I studies combined, age ranged from 18 to 65 years, with a mean age of 34.2 years. The majority of the subjects were male (72.3%), White (80.8%), and from the USA (84.4%). Most had never used or were former users of tobacco and alcohol.

8.3.2 All Phase II/III Studies Combined

Among all cethromycin-treated subjects in the Phase II/III studies combined, age ranged from 12 to 88 years, with a mean age of 46.3 years. Fifty-one subjects (1.3%) were <18 years of age; 636 (16.6%) subjects were ≥65 years of age and 187 (4.9%) subjects were ≥75 years of age. Slightly more than half of the subjects were female (51.0%) and from regions outside the USA (51.4%). The majority of the subjects were White (91.7%). Most had never used or were former users of tobacco and alcohol. Subject demographic and baseline characteristics were similar between all cethromycin-treated subjects and subjects who received active controls. In addition, subject demographic and baseline characteristics were similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

Among subjects who received cethromycin 300 mg QD in the Phase II/III studies combined, age ranged from 18 to 85 years, with a mean age of 48.5 years. One hundred fifty-three (17.6%) subjects were ≥65 years of age and 45 (5.2%) subjects were ≥75 years of age. Slightly more than half of the subjects were female (50.3%) and from regions outside the USA (61.8%). The majority of the subjects were White (87.9%). Most had never used or were former users of tobacco and alcohol. A summary of demographic and baseline characteristics in all Phase II/III studies combined is presented for selected treatment groups in Table 50.

Table 50: Demographic and Baseline Characteristics for Selected Treatment Groups (All Phase II/III Studies)

Characteristics	Cethromycin				Active Controls (N=1611)
	300 mg TDD (N=1558)	300 mg QD (N=870)	≥300 mg QD (N=1188)	All Doses (N=3836)	
Sex					
Male	779 (50.0)	432 (49.7)	590 (49.7)	1879 (49.0)	783 (48.6)
Female	779 (50.0)	438 (50.3)	598 (50.3)	1957 (51.0)	828 (51.4)
Age (years)					
Mean (SD)	46.7 (15.77)	48.5 (15.63)	48.3 (15.80)	46.3 (16.72)	47.3 (18.66)
Min, Max	18, 86	18, 85	18, 87	12, 88	12, 88
Categories					
<18	0	0	0	51 (1.3)	54 (3.4)
≥65	239 (15.3)	153 (17.6)	211 (17.8)	636 (16.6)	358 (22.2)
≥75	64 (4.1)	45 (5.2)	63 (5.3)	187 (4.9)	112 (7.0)
Race					
AI/AN	3 (0.2)	1 (0.1)	3 (0.3)	10 (0.3)	7 (0.4)
Asian	33 (2.1)	19 (2.2)	25 (2.1)	55 (1.4)	22 (1.4)
Black	109 (7.0)	57 (6.6)	71 (6.0)	198 (5.2)	58 (3.6)
White	1374 (88.2)	765 (87.9)	1061 (89.3)	3519 (91.7)	1490 (92.5)
Other	39 (2.5)	28 (3.2)	28 (2.4)	54 (1.4)	34 (2.1)
Ethnicity					
Hispanic	151 (9.7)	117 (13.4)	136 (11.4)	245 (6.4)	122 (7.6)
Non-Hispanic	446 (28.6)	446 (51.3)	446 (37.5)	446 (11.6)	442 (27.4)
NC/Missing	961 (61.7)	307 (35.3)	606 (51.0)	3145 (82.0)	1047 (65.0)
BMI (kg/m^2)	(N=1557)		(N=1186)	(N=3831)	(N=1609)
Mean (SD)	27.5 (7.57)	27.5 (6.11)	27.7 (6.23)	27.4 (6.97)	27.2 (8.38)
Min, Max	13, 195	14, 59	11, 64	5, 195	14, 253
Region					
US	657 (42.2)	332 (38.2)	539 (45.4)	1865 (48.6)	665 (41.3)
Non-US	901 (57.8)	538 (61.8)	649 (54.6)	1971 (51.4)	946 (58.7)
Tobacco Use					
Current	492 (31.6)	300 (34.5)	408 (34.3)	1220 (31.8)	510 (31.7)
Former	321 (20.6)	180 (20.7)	257 (21.6)	843 (22.0)	378 (23.5)
Never	745 (47.8)	390 (44.8)	523 (44.0)	1772 (46.2)	720 (44.7)
NC/Missing	0	0	0	1 (<0.1)	3 (0.2)
Alcohol Use					
Current	702 (45.1)	372 (42.8)	516 (43.4)	1737 (45.3)	678 (42.1)
Former	74 (4.7)	39 (4.5)	62 (5.2)	209 (5.4)	73 (4.5)
Never	774 (49.7)	458 (52.6)	609 (51.3)	1877 (48.9)	857 (53.2)
NC/Missing	8 (0.5)	1 (0.1)	1 (0.1)	13 (0.3)	3 (0.2)

mg=milligrams; TDD=total daily dose; QD=once daily; SD=standard deviation; Min, Max=minimum, maximum; AI/AN=American Indian/Alaska Native; BMI=body mass index; NC=not collected

Note: Percentages are displayed in parentheses, except where noted as SD.

8.4. Adverse Events

8.4.1 Common Adverse Events

In the analyses of treatment-emergent adverse events by preferred term, notable differences are defined as those events that have at least a 4.0 percentage point difference and at least a doubling of incidence between the treatment groups being compared.

8.4.1.1. All Phase I Studies

In the Phase I studies combined, treatment-emergent adverse events that occurred in 5% or more of all cethromycin-treated subjects included dysgeusia (22.7%), headache (14.4%), nausea (13.7%), diarrhea (8.5%), and dizziness (7.3%). Notable differences among treatment groups included:

- higher incidences of nausea and diarrhea in all cethromycin-treated subjects (13.7% and 8.5%, respectively) compared with subjects who received placebo (1.3% and 3.9%, respectively) or active controls (6.4% and 1.8%, respectively);
- a higher incidence of vomiting in all cethromycin-treated subjects (4.2%) compared with subjects who received active controls (0%);
- higher incidences of dysgeusia in all cethromycin-treated subjects (22.7%) and subjects who received active controls (19.1%) compared with placebo subjects (2.6%); and
- a higher incidence of contact dermatitis among subjects who received placebo (6.5%) compared with all cethromycin-treated subjects (2.2%) and subjects who received active controls (0%).

The incidences of specific treatment-emergent adverse events were similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD. Treatment-emergent adverse events that occurred in 5% or more of subjects who received cethromycin 300 mg QD in the Phase I studies combined included dysgeusia (20.0%), headache (14.3%), nausea (10.7%), diarrhea (7.1%), dizziness (5.5%), and rales (5.0%). The majority of the treatment-emergent adverse events reported in the Phase I studies combined were considered by the investigator to be mild or moderate in intensity. A summary of treatment-emergent adverse events experienced by ≥2.0% of subjects in selected treatment groups in all Phase I studies combined is presented in Table 51.

Table 51: Treatment-Emergent Adverse Events Experienced by ≥2.0% of Subjects in Selected Treatment Groups (All Phase I Studies)

System Organ Class Preferred Term	Placebo (N=230)	Cethromycin				Active Controls (N=110)
		300 mg TDD (N=637)	300 mg QD (N=505)	≥300 mg QD (N=675)	All Doses (N=1253)	
At Least 1 Event	**93 (40.4)**	**342 (53.7)**	**259 (51.3)**	**402 (59.6)**	**743 (59.3)**	**47 (42.7)**
Eye Disorders	4 (1.7)	3 (0.5)	2 (0.4)	7 (1.0)	9 (0.7)	3 (2.7)
Eye Pain	0	0	0	0	0	3 (2.7)
Gastrointestinal Disorders	40 (17.4)	163 (25.6)	128 (25.3)	236 (35.0)	385 (30.7)	17 (15.5)
Nausea	3 (1.3)	62 (9.7)	54 (10.7)	122 (18.1)	172 (13.7)	7 (6.4)
Diarrhea	9 (3.9)	47 (7.4)	36 (7.1)	67 (9.9)	106 (8.5)	2 (1.8)
Abdominal Pain	9 (3.9)	16 (2.5)	12 (2.4)	36 (5.3)	53 (4.2)	4 (3.6)
Vomiting	2 (0.9)	9 (1.4)	5 (1.0)	44 (6.5)	53 (4.2)	0
Abdominal Pain Upper	6 (2.6)	12 (1.9)	11 (2.2)	27 (4.0)	39 (3.1)	0
Stomach Discomfort	1 (0.4)	19 (3.0)	14 (2.8)	21 (3.1)	30 (2.4)	0
Dyspepsia	3 (1.3)	11 (1.7)	8 (1.6)	11 (1.6)	29 (2.3)	2 (1.8)
Flatulence	5 (2.2)	17 (2.7)	16 (3.2)	18 (2.7)	27 (2.2)	1 (0.9)
Constipation	5 (2.2)	14 (2.2)	9 (1.8)	9 (1.3)	21 (1.7)	1 (0.9)
Musculoskeletal and Connective Tissue Disorders	11 (4.8)	27 (4.2)	17 (3.4)	23 (3.4)	47 (3.8)	5 (4.5)
Pain in Extremity	1 (0.4)	7 (1.1)	4 (0.8)	5 (0.7)	9 (0.7)	3 (2.7)
Myalgia	5 (2.2)	1 (0.2)	1 (0.2)	2 (0.3)	4 (0.3)	1 (0.9)
Nervous System Disorders	37 (16.1)	209 (32.8)	171 (33.9)	275 (40.7)	469 (37.4)	35 (31.8)
Dysgeusia	6 (2.6)	114 (17.9)	101 (20.0)	176 (26.1)	284 (22.7)	21 (19.1)
Headache	23 (10.0)	99 (15.5)	72 (14.3)	102 (15.1)	180 (14.4)	15 (13.6)
Dizziness	9 (3.9)	34 (5.3)	28 (5.5)	51 (7.6)	92 (7.3)	9 (8.2)
Somnolence	2 (0.9)	14 (2.2)	14 (2.8)	16 (2.4)	21 (1.7)	0
Tremor	2 (0.9)	1 (0.2)	1 (0.2)	4 (0.6)	6 (0.5)	3 (2.7)
Respiratory, Thoracic and Mediastinal Disorders	10 (4.3)	56 (8.8)	44 (8.7)	51 (7.6)	112 (8.9)	3 (2.7)
Rales	0	25 (3.9)	25 (5.0)	25 (3.7)	43 (3.4)	0
Pharyngolaryngeal Pain	3 (1.3)	10 (1.6)	7 (1.4)	11 (1.6)	26 (2.1)	1 (0.9)
Skin and Subcutaneous Tissue Disorders	25 (10.9)	46 (7.2)	27 (5.3)	39 (5.8)	87 (6.9)	4 (3.6)
Dermatitis Contact	15 (6.5)	16 (2.5)	2 (0.4)	2 (0.3)	27 (2.2)	0

mg=milligrams; TDD=total daily dose; QD=once daily
Note: Percentages are displayed in parentheses.

8.4.1.2. All Phase II/III Studies

In the Phase II/III studies combined, treatment-emergent adverse events that occurred in 5% or more of all cethromycin-treated subjects included dysgeusia (7.5%), diarrhea (7.3%), nausea (6.6%), and headache (5.3%). The only notable difference observed between all cethromycin-treated subjects and subjects who received active controls was a higher incidence of dysgeusia in all cethromycin-treated subjects (7.5%) compared with subjects who received active controls (2.2%).

Although not meeting the criteria of a notable difference, the incidence of dysgeusia was higher in subjects who received cethromycin 300 mg QD compared with all cethromycin-treated subjects. The incidences of other specific treatment-emergent adverse events were similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

Treatment-emergent adverse events that occurred in 5% or more of subjects who received cethromycin 300 mg QD in the Phase II/III studies combined included dysgeusia (12.2%), diarrhea (6.9%), and nausea (6.7%). The majority of the treatment-emergent adverse events reported in the Phase II/III studies combined were considered by the investigator to be mild or moderate in intensity. A summary of treatment-emergent adverse events experienced by ≥2.0% of subjects in selected treatment groups in all Phase II/III studies combined is presented in Table 52.

Table 52: Treatment-Emergent Adverse Events Experienced by ≥2.0% of Subjects in Selected Treatment Groups (All Phase II/III Studies)

System Organ Class Preferred Term	Cethromycin				Active Controls (N=1611)
	300 mg TDD (N=1558)	300 mg QD (N=870)	≥300 mg QD (N=1188)	All Doses (N=3836)	
At Least 1 Event	721 (46.3)	420 (48.3)	645 (54.3)	1833 (47.8)	671 (41.7)
Gastrointestinal Disorders	260 (16.7)	162 (18.6)	312 (26.3)	726 (18.9)	235 (14.6)
Diarrhea	90 (5.8)	60 (6.9)	119 (10.0)	279 (7.3)	99 (6.1)
Nausea	88 (5.6)	58 (6.7)	145 (12.2)	254 (6.6)	54 (3.4)
Vomiting	46 (3.0)	32 (3.7)	80 (6.7)	125 (3.3)	22 (1.4)
Nervous System Disorders	222 (14.2)	141 (16.2)	248 (20.9)	533 (13.9)	124 (7.7)
Dysgeusia	143 (9.2)	106 (12.2)	194 (16.3)	287 (7.5)	35 (2.2)
Headache	70 (4.5)	38 (4.4)	56 (4.7)	203 (5.3)	71 (4.4)

mg=milligrams; TDD=total daily dose; QD=once daily
Note: Percentages are displayed in parentheses.

8.4.2 Deaths

Across the entire cethromycin clinical program, a total of 4 subjects who received cethromycin and 6 subjects who received active controls died due to adverse events that began after the start of study drug therapy or within 30 days after the end of study drug therapy. In addition, one cethromycin subject died from acute renal failure that started prior to beginning therapy and one active control subject died 50 days after completing study drug. All of the deaths occurred in Phase II/III studies of CAP or bronchitis. None of the adverse events that led to death were considered related to study drug. All subjects who died in the cethromycin clinical program are listed by study and treatment group in Table 53. Narratives for subjects who died are presented in Appendix A.

Table 53: Listing of Subjects Who Died by Study and Treatment Group (All Phase I, II, and III Studies)

Study #	Dose (mg)	Subject	Age/ Sex	Preferred Term	Start Day[a]	Stop Day[a]	Severity/ Relationship
Phase II/III Studies: Cethromycin							
CL05-001	300 QD	3006-0089	58/M	Acute Myocardial Infarction	6 (1)	6 (1)	Severe/ Not Related
CL06-001	300 QD	5606-00001	52/M	Small Cell Lung Cancer Stage Unspecified	7	21 (14)	Severe/ Not Related
				Haemoptysis	7	21 (14)	Severe/ Not Related
M00-217	150 QD	17454-21391	76/M	Renal Failure Acute	-8	3 (1)	Severe/ Not Related
M00-219	150 QD	18387-34086	65/M	Cyanosis	4 (1)	4 (1)	Severe/ Not Related
				Confusional State	4 (1)	4 (1)	Severe/ Not Related
				Disorientation	4 (1)	4 (1)	Severe/ Not Related
				Restlessness	4 (1)	4 (1)	Severe/ Not Related
	150 BID	18493-34045	40/M	Pneumonia	11 (7)	12 (8)	Severe/ Not Related
Phase II/III Studies: Active Controls							
CL05-001 Clari	250 BID	2011-0036	66/F	Lung Squamous Cell Carcinoma Stage Unspecified	14 (7)	57 (50)	Moderate/ Not Related
				Pneumothorax	14 (7)	57 (50)	Moderate/ Not Related
				Arrhythmia	57 (50)	59 (52)	Severe/ Not Related
				Cardiac Arrest	57 (50)	59 (52)	Severe/ Not Related
		3004-0013	59/M	Pneumonia	5 (2)	5 (2)	Severe/ Probably Not Related
		3006-0056	79/F	Angina Pectoris	4	5 (1)	Severe/ Not Related
				Acute Myocardial Infarction	5 (1)	5 (1)	Severe/ Not Related
CL06-001 Clari	250 BID	5704-00001	71/M	Lung Neoplasm Malignant	4	19 (14)	Severe/ Not Related
M00-216 Azith	250 QD	9773-20780	64/M	Chronic Obstructive Pulmonary Disease	1	18 (17)	Moderate/ Not Related
		9625-20933	81/F	Muscle Haemorrhage	13 (10)	14 (11)	Severe/ Not Related
M00-217 Levo	500 QD	17677-21188	87/F	Myocardial Infarction	23 (16)	26 (19)	Severe/ Not Related
				Myocardial Ischaemia	23 (16)	26 (19)	Severe/ Not Related

mg=milligrams; QD=once daily; BID=twice daily; M=male; F=female; Clari=clarithromycin; Azith=azithromycin; Levo=levofloxacin

a Numbers in parentheses are days relative to the last dose of study drug.

8.4.3 Other Serious Adverse Events

Serious adverse events are generally defined as any adverse event which meets one of the following criteria:

- Results in death of subject
- Is considered life-threatening
- Results in hospitalization or prolongation of hospitalization
- Is considered an important medical event requiring medical or surgical intervention to prevent a serious outcome
- Results in a persistent or significant disability or incapacity

8.4.3.1. All Phase I Studies

Among all cethromycin-treated subjects in the Phase I studies combined, 4 (0.3%) subjects experienced treatment-emergent serious adverse events. Of these four subjects, two received 300 mg QD, one received 150 mg QD, and one received 600 mg QD. The events reported included severe schizoaffective disorder, moderate pneumonitis, severe urticaria, and moderate pyrexia. None of the subjects who received placebo or active controls in the Phase I studies combined experienced a treatment-emergent serious adverse event. Of the four treatment-emergent serious adverse events experienced in cethromycin-treated subjects in all Phase I studies combined, only one was considered related to study drug. Subject 12884-00018 was a 35-year-old male who developed severe urticaria on Day 2 of dosing with cethromycin 600 mg QD. The event resolved after 5 hours and was considered serious as it prolonged hospitalization. The subject was discontinued from study due to the event and was treated with betamethasone-dexchlorpheniramine and cetirizine.

8.4.3.2. All Phase II/III Studies

Among all cethromycin-treated subjects in the Phase II/III studies combined, 93 (2.4%) experienced at least one treatment-emergent serious adverse event; this incidence was similar to that observed for subjects who received active controls (2.6%). All of the specific treatment-emergent serious adverse events reported among all cethromycin-treated subjects in the Phase II/III studies combined had an incidence of ≤0.1%, except for pneumonia (0.5%), which was the underlying disease being treated for the majority of the subjects who reported this event. The majority of the treatment-emergent serious adverse events reported were considered by the investigator to be severe in intensity.

No notable differences were observed with respect to the types of treatment-emergent serious adverse events reported among all cethromycin-treated subjects or subjects who received active controls. The incidences of specific treatment-emergent serious adverse events were similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

Among subjects who received cethromycin 300 mg QD in the Phase II/III studies combined, 38 (4.4%) experienced at least 1 treatment-emergent serious adverse event. All of the specific treatment-emergent serious adverse events reported among subjects who received cethromycin 300 mg QD had an incidence of ≤0.1%, except for pneumonia (0.8%), atrial fibrillation (0.2%),

cardiac failure congestive (0.2%), and deep vein thrombosis (0.2%). A summary of treatment-emergent serious adverse events experienced by ≥2 subjects in selected treatment groups in all Phase II/III studies combined is presented in Table 54.

Table 54: Treatment-Emergent Serious Adverse Events Experienced by ≥2 Subjects in Selected Treatment Groups (All Phase II/III Studies)

System Organ Class Preferred Term	Cethromycin				Active Controls (N=1611)
	300 mg TDD (N=1558)	300 mg QD (N=870)	≥300 mg QD (N=1188)	All Doses (N=3836)	
Cardiac Disorders	**7 (0.4)**	**7 (0.8)**	**8 (0.7)**	**11 (0.3)**	**5 (0.3)**
Atrial Fibrillation	2 (0.1)	2 (0.2)	2 (0.2)	2 (0.1)	0
Cardiac Failure Congestive	2 (0.1)	2 (0.2)	2 (0.2)	2 (0.1)	1 (0.1)
Gastrointestinal Disorders	**4 (0.3)**	**2 (0.2)**	**3 (0.3)**	**6 (0.2)**	**2 (0.1)**
Vomiting	1 (0.1)	0	0	2 (0.1)	1 (0.1)
General Disorders and Administration Site Conditions	**0**	**0**	**1 (0.1)**	**1 (<0.1)**	**2 (0.1)**
Chest Pain	0	0	0	0	2 (0.1)
Infections and Infestations	**20 (1.3)**	**11 (1.3)**	**14 (1.2)**	**38 (1.0)**	**18 (1.1)**
Pneumonia	13 (0.8)	7 (0.8)	9 (0.8)	21 (0.5)	5 (0.3)
Bronchitis Acute	0	0	0	2 (0.1)	3 (0.2)
Empyema	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)
Lung Abscess	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)	0
Lobar Pneumonia	1 (0.1)	0	0	1 (<0.1)	4 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	**15 (1.0)**	**11 (1.3)**	**13 (1.1)**	**26 (0.7)**	**6 (0.4)**
Asthma	2 (0.1)	0	0	3 (0.1)	1 (0.1)
Chronic Obstructive Pulmonary Disease	1 (0.1)	1 (0.1)	1 (0.1)	3 (0.1)	5 (0.3)
Dyspnoea	2 (0.1)	1 (0.1)	1 (0.1)	3 (0.1)	0
Pleural Effusion	2 (0.1)	1 (0.1)	2 (0.2)	3 (0.1)	0
Hypoxia	0	0	1 (0.1)	2 (0.1)	0
Vascular Disorders	**2 (0.1)**	**2 (0.2)**	**2 (0.2)**	**5 (0.1)**	**1 (0.1)**
Deep Vein Thrombosis	2 (0.1)	2 (0.2)	2 (0.2)	4 (0.1)	0

mg=milligrams; TDD=total daily dose; QD=once daily
Note: Percentages are displayed in parentheses.

Of the 93 cethromycin–treated subjects who experienced treatment-emergent serious adverse events in all Phase II/III studies combined, 5 had events that were considered related to study drug. The drug-related, treatment-emergent serious adverse events reported were epistaxis, facial palsy, cardiogenic shock, vomiting, deep vein thrombosis, and phlebitis.

Of the 42 active control–treated subjects who experienced treatment-emergent serious adverse events in all Phase II/III studies combined, 3 had events that were considered related to study drug. The drug-related, treatment-emergent serious adverse events reported were hepatitis C, dermatitis allergic, and drug hypersensitivity.

8.4.4 Adverse Events Resulting in Discontinuation

8.4.4.1. All Phase I Studies

Among all cethromycin-treated subjects in the Phase I studies combined, 15 (1.2%) subjects experienced treatment-emergent adverse events resulting in discontinuation. Of these, 7 received 300 mg QD, 4 received 150 mg BID, 1 received 100 mg TID, 1 received 600 mg QD, and 2 received 450 mg BID. The majority of the treatment-emergent adverse events resulting in discontinuation were considered by the investigator to be mild or moderate in intensity. One subject who received placebo in the Phase I studies combined experienced a treatment-emergent adverse event resulting in discontinuation (urticaria); none of the subjects who received active controls experienced a treatment-emergent adverse event resulting in discontinuation. No notable differences were observed for the incidences of specific treatment-emergent adverse events resulting in discontinuation between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

Of the 15 cethromycin–treated subjects who experienced treatment-emergent adverse events resulting in discontinuation in all Phase I studies combined, 8 had events that were considered related to study drug. The most common drug-related, treatment-emergent adverse events resulting in discontinuation in cethromycin-treated subjects were associated with abnormal laboratory tests, specifically hepatic enzyme increased (4 subjects; 0.3%) and transaminases increased (1 subject; 0.1%).

Four cethromycin subjects, two who received 150 mg BID and two who received 450 mg BID, in Study M01-325 were discontinued due to elevated liver enzymes that were judged by the investigator as adverse events. All of the events were asymptomatic, self-limiting transaminase elevations (ALT or aspartate aminotransferase [AST] >3 × ULN), which returned to within normal limits, without intervention, within 2-4 weeks. Transaminase elevations were accompanied by increased gamma glutamyl transferase (GGT), alkaline phosphatase, or lactate dehydrogenase (LDH) values in some cases, but no abnormalities in total bilirubin were observed. One of the subjects was subsequently found to have cholelithiasis with a stone at the level of the common bile duct on hepatic ultrasound. One cethromycin subject who received 300 mg QD in Study M99-016 was discontinued due to an event of increased ALT (170 U/L) that started 8 days after dosing in Period 1 (Day 13). Follow-up values showed a steady decline in ALT, with a normal value obtained on Day 23 (33 U/L).

8.4.4.2. All Phase II/III Studies

Among all cethromycin-treated subjects in the Phase II/III studies combined, 122 (3.2%) experienced at least one treatment-emergent adverse event resulting in discontinuation; this incidence was similar to that observed for subjects who received active controls (3.4%). The most common treatment-emergent adverse events resulting in discontinuation among all cethromycin-treated subjects were gastrointestinal disorders, specifically nausea (0.7%), vomiting (0.5%), diarrhea (0.4%), and abdominal pain (0.2%); pneumonia (0.4%); and headache (0.2%). The incidences of these events were generally similar to those observed in subjects who received active controls. All of the remaining treatment-emergent adverse events resulting in discontinuation reported among all cethromycin-treated subjects had an incidence of ≤0.1%. The

majority of the treatment-emergent adverse events resulting in discontinuation were considered by the investigator to be mild or moderate in intensity.

No notable differences were observed with respect to the types of treatment-emergent adverse events resulting in discontinuation among all cethromycin-treated subjects or subjects who received active controls. The incidences of specific treatment-emergent adverse events resulting in discontinuation were similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

Among subjects who received cethromycin 300 mg QD in the Phase II/III studies combined, 22 (2.5%) experienced at least one treatment-emergent adverse event resulting in discontinuation. The most common treatment-emergent adverse events resulting in discontinuation experienced by subjects who received cethromycin 300 mg QD were gastrointestinal disorders, specifically nausea (0.6%), vomiting (0.6%), abdominal pain (0.3%), and diarrhea (0.2%); pneumonia (0.6%); dysgeusia (0.2%); and wheezing (0.2%). All of the remaining treatment-emergent adverse events resulting in discontinuation reported among subjects who received cethromycin 300 mg QD had an incidence of ≤0.1%. A summary of treatment-emergent adverse events experienced by ≥2 subjects in selected treatment groups that resulted in discontinuation in all Phase II/III studies combined is presented in Table 55.

Table 55: Treatment-Emergent Adverse Events Resulting in Discontinuation Experienced by ≥2 Subjects in Selected Treatment Groups (All Phase II/III Studies)

System Organ Class Preferred Term	Cethromycin				Active Controls (N=1611)
	300 mg TDD (N=1558)	300 mg QD (N=870)	≥300 mg QD (N=1188)	All Doses (N=3836)	
Gastrointestinal Disorders	**14 (0.9)**	**9 (1.0)**	**30 (2.5)**	**50 (1.3)**	**18 (1.1)**
Nausea	7 (0.4)	5 (0.6)	20 (1.7)	28 (0.7)	9 (0.6)
Vomiting	6 (0.4)	5 (0.6)	17 (1.4)	21 (0.5)	3 (0.2)
Diarrhea	2 (0.1)	2 (0.2)	8 (0.7)	17 (0.4)	8 (0.5)
Abdominal Pain	4 (0.3)	3 (0.3)	5 (0.4)	6 (0.2)	3 (0.2)
Abdominal Pain Upper	0	0	1 (0.1)	4 (0.1)	0
Abdominal Discomfort	1 (0.1)	1 (0.1)	1 (0.1)	3 (0.1)	1 (0.1)
General Disorders and Administration Site Conditions	**2 (0.1)**	**0**	**2 (0.2)**	**5 (0.1)**	**2 (0.1)**
Fatigue	1 (0.1)	0	0	2 (0.1)	0
Immune System Disorders	**0**	**0**	**1 (0.1)**	**3 (0.1)**	**5 (0.3)**
Hypersensitivity	0	0	1 (0.1)	2 (0.1)	2 (0.1)
Drug Hypersensitivity	0	0	0	1 (<0.1)	3 (0.2)
Infections and Infestations	**12 (0.8)**	**5 (0.6)**	**10 (0.8)**	**35 (0.9)**	**12 (0.7)**
Pneumonia	7 (0.4)	5 (0.6)	8 (0.7)	15 (0.4)	2 (0.1)
Bronchitis Acute	0	0	0	3 (0.1)	1 (0.1)
Gastroenteritis	0	0	1 (0.1)	2 (0.1)	1 (0.1)
Urinary Tract Infection	2 (0.1)	0	0	2 (0.1)	0
Vulvovaginal Mycotic Infection	1 (0.1)	0	0	2 (0.1)	0
Lobar Pneumonia	0	0	0	1 (<0.1)	2 (0.1)
Investigations	**3 (0.2)**	**2 (0.2)**	**2 (0.2)**	**6 (0.2)**	**3 (0.2)**
Hepatic Enzyme Increased	0	0	0	2 (0.1)	1 (0.1)
Nervous System Disorders	**5 (0.3)**	**3 (0.3)**	**8 (0.7)**	**16 (0.4)**	**7 (0.4)**
Headache	1 (0.1)	0	1 (0.1)	6 (0.2)	3 (0.2)
Dysgeusia	3 (0.2)	2 (0.2)	4 (0.3)	5 (0.1)	2 (0.1)
Hypoaesthesia	0	0	1 (0.1)	2 (0.1)	0
Psychiatric Disorders	**1 (0.1)**	**1 (0.1)**	**1 (0.1)**	**3 (0.1)**	**1 (0.1)**
Restlessness	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)	0
Renal and Urinary Disorders	**0**	**0**	**0**	**2 (0.1)**	**0**
Renal Pain	0	0	0	2 (0.1)	0

mg=milligrams; TDD=total daily dose; QD=once daily
Note: Percentages are displayed in parentheses.

Table 55: Treatment-Emergent Adverse Events Resulting in Discontinuation Experienced by ≥2 Subjects in Selected Treatment Groups (All Phase II/III Studies) (continued)

System Organ Class Preferred Term	Cethromycin				Active Controls (N=1611)
	300 mg TDD (N=1558)	300 mg QD (N=870)	≥300 mg QD (N=1188)	All Doses (N=3836)	
Respiratory, Thoracic and Mediastinal Disorders	**7 (0.4)**	**4 (0.5)**	**6 (0.5)**	**16 (0.4)**	**3 (0.2)**
Asthma	2 (0.1)	0	0	3 (0.1)	0
Dyspnoea	1 (0.1)	0	0	2 (0.1)	0
Epistaxis	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)	0
Wheezing	2 (0.1)	2 (0.2)	2 (0.2)	2 (0.1)	0
Chronic Obstructive Pulmonary Disease	0	0	0	0	2 (0.1)
Skin and Subcutaneous Tissue Disorders	**3 (0.2)**	**1 (0.1)**	**3 (0.3)**	**8 (0.2)**	**6 (0.4)**
Dermatitis Allergic	1 (0.1)	0	1 (0.1)	3 (0.1)	1 (0.1)
Hyperhidrosis	1 (0.1)	1 (0.1)	2 (0.2)	3 (0.1)	0
Urticaria	1 (0.1)	0	0	2 (0.1)	2 (0.1)

mg=milligrams; TDD=total daily dose; QD=once daily
Note: Percentages are displayed in parentheses.

8.5. Clinical Laboratory Evaluations

8.6. Hematology

8.6.1 Possibly Clinically Significant Hematology Values

The definitions of possibly clinically significant hematology values are presented in Table 56.

Table 56: Possibly Clinically Significant Hematology Values

Variable	Criterion Values SI Units
Hematology	
Hematocrit	Male: ≤37%; Female: ≤32%
Hemoglobin	Male: ≤11.5 g/dL; Female: ≤9.5 g/dL
Platelets	$\leq 75 \times 10^9$/L or $\geq 700 \times 10^9$/L
White Blood Cells	$\leq 2.8 \times 10^9$/L or $\geq 16 \times 10^9$/L
Monocytes	≥15%
Eosinophils	≥10%
Red Blood Cells	Male: $\leq 3.8 \times 10^{12}$/L; Female: $\leq 3.5 \times 10^{12}$/L or Male: $\geq 7.0 \times 10^{12}$/L; Female: $\geq 6.0 \times 10^{12}$/L

8.6.1.1. All Phase I Studies Combined

In the Phase I studies combined, no notable differences were observed for the incidences of possibly clinically significant hematology values between all cethromycin-treated subjects and subjects who received placebo or active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant hematology values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

8.6.1.2. All Phase II/III Studies Combined

In the Phase II/III studies combined, no notable differences were observed for the incidences of possibly clinically significant hematology values between all cethromycin-treated subjects and subjects who received active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant hematology values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

In the Phase II/III studies combined, the incidences of treatment-emergent possibly clinically significant hematology values were similar among the cethromycin dose groups (<300 mg TDD, 300 mg TDD, 300 mg QD, and >300 mg TDD) with no notable differences observed with respect to increasing dose.

8.6.2 Mean Change From Baseline

In the Phase II/III studies combined, mean changes from baseline to the final on-therapy visit or the final off-therapy visit in hematology values were generally small, and no discernable trends were observed between all cethromycin-treated subjects and subjects who received active

controls. Consistent with resolving infection, subjects who received cethromycin or active controls demonstrated mean decreases in WBCs and neutrophils. In addition, no discernable trends were observed in mean changes from baseline in hematology values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

8.6.3 Shifts From Baseline

In the Phase II/III studies combined, no notable differences were observed for the incidences of shifts from normal baseline to the greatest deviation in post-baseline hematology values between all cethromycin-treated subjects and subjects who received active controls. Similarly, no notable differences were observed for the incidences of shifts from normal baseline to the greatest deviation in post-baseline hematology values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

8.7. Clinical Chemistry

8.7.1 Possibly Clinically Significant Chemistry Values

The definitions of possibly clinically significant chemistry values are presented in Table 57.

Table 57: Possibly Clinically Significant Chemistry Values

Variable	Criterion Values
	SI Units
Blood Chemistry	
AST (SGOT)	≥3 × ULN
ALT (SGPT)	≥3 × ULN
GGT	≥3 × ULN
Alkaline Phosphatase	≥3 × ULN
BUN	≥10.7 μM
Creatinine	≥176.8 μM
Uric Acid	Male: ≥624.6 μM; Female: ≥505.6 μM
Total Bilirubin	≥1.5 × ULN
Direct Bilirubin	≥8.55 μmol/L
Albumin	≤25 g/L

AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma glutamyl transferase, BUN = blood urea nitrogen; ULN = upper limit of normal

8.7.1.1. All Phase I Studies Combined

In the Phase I studies combined, the only notable difference observed between all cethromycin-treated subjects and subjects who received placebo or active controls was for the incidences of possibly clinically significant increases in direct bilirubin values, which were higher in subjects who received active controls (4.26%) compared to all cethromycin-treated subjects (1.36%) and subjects who received placebo (0%). The incidences of possibly clinically significant chemistry values were similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

8.7.1.2. All Phase II/III Studies Combined

In the Phase II/III studies combined, no notable differences were observed for the incidences of possibly clinically significant chemistry values between all cethromycin-treated subjects and subjects who received active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant chemistry values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD. Although not meeting the criteria of a notable difference, the incidences of increases in AST and ALT values were slightly higher in all cethromycin-treated subjects (1.02% and 1.30%, respectively) compared to active controls (0.33% and 0.73%, respectively); greater numbers of subjects who received cethromycin 300 mg QD had increases in these values (1.95% and 2.97%, respectively) compared to all cethromycin-treated subjects. A summary of treatment-emergent possibly clinically significant AST and ALT values in all Phase II/III studies combined is presented for selected treatment groups in Table 58.

Table 58: Treatment-Emergent Possibly Clinically Significant AST and ALT Values for Selected Treatment Groups (All Phase II/III Studies)

Variable (PCS Criteria)	Cethromycin				Active Controls (N=1611)
	300 mg TDD (N=1558)	300 mg QD (N=870)	≥300 mg QD (N=1188)	All Doses (N=3836)	
AST (≥3 × ULN)	20/1431 (1.40)	15/770 (1.95)	17/1065 (1.60)	37/3624 (1.02)	5/1493 (0.33)
ALT (≥3 × ULN)	28/1435 (1.95)	23/774 (2.97)	26/1071 (2.43)	47/3629 (1.30)	11/1499 (0.73)

PCS=possibly clinically significant; mg=milligrams; TDD=total daily dose; QD=once daily; AST=aspartate aminotransferase; ALT=alanine aminotransferase
Note: Percentages are displayed in parentheses.

8.7.2 Mean Change From Baseline

In the Phase II/III studies combined, mean changes from baseline to the final on-therapy visit or the final off-therapy visit in chemistry values were generally small among all cethromycin-treated subjects and subjects who received active controls. Slight trends were observed in mean changes from baseline to the final on-therapy visit in ALT, creatinine, and uric acid values. Among all cethromycin-treated subjects, the mean increases in ALT, creatinine, and uric acid values at the final on-therapy visit were 3.83 U/L, 2.048 µmol/L, and 11.539 µmol/L, respectively, compared with an increase in ALT of 1.599 U/L and decreases in creatinine and uric acid of -3.187 µmol/L and -14.336 µmol/L for subjects who received active controls. Mean changes from baseline at the final off-therapy visit were similar between cethromycin and active control subjects for these variables.

Compared to all cethromycin-treated subjects, subjects who received cethromycin 300 mg QD had higher mean increases in ALT values (6.793 vs. 3.83 U/L) at the final on-therapy visit; however, similar mean decreases in ALT values were noted in both groups at the final off-therapy visit. A summary of mean changes from baseline to the final on-therapy visit and final off-therapy visit in chemistry values in all Phase II/III studies combined is presented for selected treatment groups in Table 59.

Table 59: Mean Changes from Baseline to Final On-Therapy Visit and Final Off-Therapy Visit in ALT, Creatinine, and Uric Acid Values for Selected Treatment Groups (All Phase II/III Studies)

Variable	Cethromycin				Active Controls (N=1611)
	300 mg TDD (N=1558)	300 mg QD (N=870)	≥300 mg QD (N=1188)	All Doses (N=3836)	
ALT (U/L)					
Final On-Therapy Visit	(N=553)	(N=473)	(N=495)	(N=881)	(N=628)
Mean Baseline (SD)	28.396 (23.02)	28.539 (21.79)	28.739 (21.79)	26.67 (26.52)	26.438 (27.87)
Mean Change (SD)	6.166 (27.67)	6.793 (28.58)	6.62 (28.16)	3.83 (24.43)	1.599 (20.42)
Final Off-Therapy Visit	(N=1391)	(N=752)	(N=1040)	(N=3508)	(N=1469)
Mean Baseline (SD)	26.135 (29.40)	27.754 (19.86)	27.596 (19.89)	23.747 (26.35)	22.062 (22.60)
Mean Change (SD)	-1.493 (27.99)	-1.182 (17.38)	-0.388 (17.19)	-1.189 (22.67)	-1.245 (15.45)
Creatinine (µmol/L)					
Final On-Therapy Visit	(N=555)	(N=479)	(N=502)	(N=878)	(N=635)
Mean Baseline (SD)	81.038 (26.19)	80.909 (24.79)	80.457 (24.55)	79.204 (26.01)	79.684 (52.19)
Mean Change (SD)	2.865 (21.07)	2.863 (20.34)	3.147 (20.10)	2.048 (20.60)	-3.187 (19.91)
Final Off-Therapy Visit	(N=1408)	(N=764)	(N=1058)	(N=3546)	(N=1478)
Mean Baseline (SD)	77.924 (22.68)	76.82 (22.87)	76.237 (23.75)	76.254 (21.34)	76.475 (36.57)
Mean Change (SD)	-2.28 (17.14)	-2.967 (18.15)	-2.555 (17.52)	-1.202 (15.49)	-2.053 (29.56)
Uric Acid (µmol/L)					
Final On-Therapy Visit	(N=554)	(N=479)	(N=502)	(N=875)	(N=635)
Mean Baseline (SD)	298.289 (96.19)	295.304 (95.53)	296.282 (95.05)	296.136 (94.55)	314.342 (376.99)
Mean Change (SD)	9.065 (61.09)	9.796 (60.53)	10.05 (59.85)	11.539 (59.33)	-14.336 (369.23)
Final Off-Therapy Visit	(N=1406)	(N=764)	(N=1058)	(N=3541)	(N=1478)
Mean Baseline (SD)	303.233 (93.81)	298.624 (96.04)	302.753 (94.26)	303.029 (91.83)	309.646 (256.54)
Mean Change (SD)	15.954 (64.32)	17.054 (62.43)	15.131 (62.60)	15.885 (61.83)	6.07 (247.35)

mg=milligrams; TDD=total daily dose; QD=once daily; ALT=alanine aminotransferase; SD=standard deviation

8.7.3 Shifts From Baseline

Additional information regarding shifts from normal baseline values to post-baseline values in hepatic function tests including ALT, AST, GGT, alkaline phosphatase, and total bilirubin are presented in Section 8.11.1.

In the Phase II/III studies combined, no notable differences were observed for the incidences of shifts from normal baseline to the greatest deviation in post-baseline chemistry values between all cethromycin-treated subjects and subjects who received active controls. Although not meeting the criteria of a notable difference, the incidence of shifts from normal baseline to above the normal range in creatinine values was higher among all cethromycin-treated subjects compared with subjects who received active controls.

Notable differences were observed for shifts from normal baseline to below the normal range for calcium values and to above the normal range for chloride values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD, with greater incidences of these shifts observed among all cethromycin-treated subjects (5.72% and 5.81%, respectively) compared to subjects who received cethromycin 300 mg QD (2.86% and 0.46%, respectively). Although not meeting the criteria of a notable difference, the incidence of shifts from normal baseline to above the normal range in ALT and AST values was higher among subjects who received cethromycin 300 mg QD compared with all cethromycin-treated subjects. A summary of shifts from baseline to the greatest deviation in post-baseline ALT, AST, calcium, chloride, and creatinine values in all Phase II/III studies combined is presented for selected treatment groups in Table 60.

Table 60: Shifts From Normal Baseline to Greatest Deviation in Post-Baseline ALT, AST, Calcium, Chloride and Creatinine Values for Selected Treatment Groups (All Phase II/III Studies)

Variable	Cethromycin				Active Controls (N=1611)
	300 mg TDD (N=1558)	300 mg QD (N=870)	≥300 mg QD (N=1188)	All Doses (N=3836)	
ALT (U/L)					
Below LLN	4 (0.26)	1 (0.12)	1 (0.08)	6 (0.16)	0 (0.00)
Above ULN	204 (15.50)	131 (17.85)	173 (17.11)	412 (12.41)	149 (10.41)
AST (U/L)					
Below LLN	2 (0.13)	2 (0.23)	3 (0.25)	9 (0.24)	4 (0.25)
Above ULN	132 (9.68)	91 (12.01)	123 (11.80)	297 (8.73)	106 (7.25)
Calcium (mmol/L)					
Below LLN	79 (5.29)	24 (2.86)	41 (3.61)	209 (5.72)	70 (4.49)
Above ULN	37 (2.41)	8 (0.92)	8 (0.67)	104 (2.77)	41 (2.61)
Chloride (mmol/L)					
Below LLN	26 (1.71)	7 (0.82)	10 (0.85)	106 (2.84)	51 (3.35)
Above ULN	63 (4.12)	4 (0.46)	6 (0.51)	217 (5.81)	108 (6.87)
Creatinine (μmol/L)					
Below LLN	3 (0.19)	1 (0.12)	2 (0.17)	6 (0.16)	3 (0.19)
Above ULN	97 (6.67)	60 (7.35)	81 (7.26)	185 (5.09)	46 (2.99)

mg=milligrams; TDD=total daily dose; QD=once daily; ALT=alanine aminotransferase; LLN=lower limit of normal; ULN=upper limit of normal; AST=aspartate aminotransferase
Note: Percentages are displayed in parentheses.

8.8. Urinalysis

8.8.1 Possibly Clinically Significant Urinalysis Values

The definitions of possibly clinically significant urinalysis values are presented in Table 61.

Table 61: Possibly Clinically Significant Urinalysis Values

Variable	Criterion Values
	SI Units
pH	<5 or >8
Specific Gravity	<1.003 or >1.035

8.8.1.1. All Phase I Studies Combined

In the Phase I studies combined, no notable differences were observed for the incidences of possibly clinically significant urinalysis values between all cethromycin-treated subjects and subjects who received placebo or active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant urinalysis values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

8.8.1.2. All Phase II/III Studies Combined

In the Phase II/III studies combined, no notable differences were observed for the incidences of possibly clinically significant urinalysis values between all cethromycin-treated subjects and subjects who received active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant urinalysis values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

In the Phase II/III studies combined, the incidences of treatment-emergent possibly clinically significant urinalysis values were similar among the cethromycin dose groups (<300 mg TDD, 300 mg TDD, 300 mg QD, and >300 mg TDD), with no notable differences observed with respect to increasing dose.

8.8.2 Mean Change From Baseline

In the Phase II/III studies combined, mean changes from baseline to the final on-therapy visit or the final off-therapy visit in urinalysis values were generally small, and no discernable trends were observed between all cethromycin-treated subjects and subjects who received active controls. In addition, no discernable trends were observed in mean changes from baseline in urinalysis values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

8.9. Vital Signs

In the analyses of vital sign parameters, notable differences for possibly clinically significant values and shifts from baseline are defined as those events that have at least a 2.0 percentage point difference and at least a doubling of incidence between the treatment groups being compared. Any trends noted with respect to mean changes from baseline are discussed.

8.9.1 Possibly Clinically Significant Values for Vital Sign Parameters

The definitions of possibly clinically significant vital signs values are presented in Table 62.

Table 62: Possibly Clinically Significant Vital Signs Values

Vital Sign	Direction	Criterion
Systolic Blood Pressure	Low	Value ≤90 mmHg and decreased ≥20 mmHg from initial value
	High	Value ≥180 mmHg and increased ≥20 mmHg from initial value
Diastolic Blood Pressure	Low	Value ≤50 mmHg and decreased ≥15 mmHg from initial value
	High	Value ≥105 mmHg and increased ≥15 mmHg from initial value
Pulse	Low	Value ≤50 bpm and decreased ≥15 bpm from initial value
	High	Value ≥120 bpm and increased ≥15 bpm from initial value
Temperature		Change of ≥2° F or change of ≥1.1° C

8.9.1.1. All Phase I Studies Combined

In the Phase I studies combined, no notable differences were observed between all cethromycin-treated subjects and subjects who received placebo for the incidences of possibly clinically significant vital signs values. However, a notable difference was observed between all cethromycin-treated subjects and subjects who received active controls for the incidence of possibly clinically significant increases in temperature, which was higher in all cethromycin-treated subjects (5.03%) compared to subjects who received active controls (0%). The incidences of possibly clinically significant vital signs values were similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

8.9.1.2. All Phase II/III Studies Combined

In the Phase II/III studies combined, no notable differences were observed for the incidences of possibly clinically significant vital signs values between all cethromycin-treated subjects and subjects who received active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant vital signs values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

In the Phase II/III studies combined, the incidences of treatment-emergent possibly clinically significant vital sign values were similar among the cethromycin dose groups (<300 mg TDD, 300 mg TDD, 300 mg QD, and >300 mg TDD), with no notable differences observed with respect to increasing dose.

8.9.2 Mean Change From Baseline in Vital Sign Parameters

In the Phase II/III studies combined, mean changes from baseline to the final on-therapy visit or the final off-therapy visit in vital signs values were generally small, and no discernable trends were observed between all cethromycin-treated subjects and subjects who received active controls. In addition, no discernable trends were observed in mean changes from baseline in vital signs values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

8.10. Electrocardiograms

Advanced Life Sciences conducted a "thorough QT/QT_C study" (CL07-001) following the International Conference on Harmonization E14 guidance for clinical evaluation of QT/QT_C interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (Section 8.10.1). Results of the pooled analyses for the Phase I studies, the Phase II/III studies, and the two Phase III controlled CAP studies are presented in Section 8.10.2.

8.10.1 Thorough QT/QT_C Study

Study CL07-001 was a Phase I, randomized, double-blind (except for the use of moxifloxacin), placebo and positive-controlled, multiple-dose, single-site, 4-arm, parallel-design using healthy adult male and female subjects 18-45 years of age, inclusive, to evaluate the effect of cethromycin on cardiac repolarization, as detected by QT/ QT_C prolongation in healthy subjects. Two hundred thirty-eight subjects participated and were randomized to receive 1 of the following 4 treatment regimens:

Treatment A: Placebo from Day 1 through Day 5.

Treatment B: Placebo from Day 1 through Day 4, and 400 mg moxifloxacin on Day 5.

Treatment C: Cethromycin 300 mg QD from Day 1 through Day 5.

Treatment D: Cethromycin 900 mg QD from Day 1 through Day 5.

Electrocardiograms were obtained using a 12-lead continuous digital recorder on Day -1 (baseline) and on Day 5. A total of 39 ECGs were analyzed at baseline and on Day 5, for a total of 78 ECGs in each completed subject. Blood was obtained for pharmacokinetic sampling on Days 1 and 5.

Of the 238 subjects who participated in the study, 233 completed the study as planned. Three subjects (cethromycin 900 mg) prematurely discontinued due to adverse events, one subject (cethromycin 300 mg) was discontinued by the investigator due to abnormal laboratory results, and one subject (cethromycin 900 mg) withdrew due to personal reasons.

The primary endpoint was the QT_CI. The mean change from baseline for the QT_CI duration placebo-corrected using the time averaged analysis showed +1 msec for the clinical dose and +3 msec for the supratherapeutic dose of cethromycin. Using the time matched primary analysis endpoint; no time point in the cethromycin dose groups showed an upper bound that was ≥10 msec. The specific outlier criteria included a new >500 msec QT_CI, a change from baseline of >60 msec or new abnormal U waves. No subject on cethromycin showed any of these criteria. The nonspecific criterion of a 30-60 msec change from baseline was seen in 2% on placebo, 7% on moxifloxacin, and in 2% of cethromycin subjects on either dose. No new morphological changes in this trial were observed except for the non-specific change in T-wave morphology which was observed in 3.4% on placebo, 3.4% on moxifloxacin, 0% on 300 mg cethromycin, and 1.8% on 900 mg cethromycin. There were no statistically significant differences between the sub-groupings by gender in this study.

The relationship between plasma concentrations of parent and metabolite and change in QT_CI revealed no evidence of any signal that cethromycin concentration or metabolite were related to observed QT_CI changes. The mean change from baseline in placebo-corrected heart rate for the moxifloxacin group was 1 bpm and for the clinical cethromycin dose group it was 12 bpm; neither change was clinically relevant. For the supratherapeutic dose of cethromycin, the heart rate change was 10 bpm which was clinically relevant and was associated with more tachycardic outliers (13%) compared to placebo (7%) and the clinical cethromycin dose (3%). Thus, the supratherapeutic dose does have a heart rate effect (marked increase) that prohibits use of the Bazett-corrected QT_C (QT_CB) due to its known high degree of inaccuracy for drugs with this heart rate effect. The mean change from baseline placebo-corrected for PR interval for the moxifloxacin group and the clinical and supratherapeutic dose cethromycin groups were

approximately -1, 0, and 0 msec, respectively; similarly for the QRS they were 0, -1, and -1 msec, respectively.

The results of this thorough ECG trial showed no signal of any effect on AV conduction, depolarization or cardiac repolarization as measured by the PR, QRS, QT_CI, or QT_CF interval durations. There was no effect on heart rate in the clinical dose at steady state on cethromycin, though in the supratherapeutic dose group, there was a 10 bpm increase requiring use of the primary QT_CI endpoint, or QT_CF, but not QT_CB for detection of any effect on cardiac repolarization. Cethromycin did not show any signal of any outlier imbalance. No changes in ECG wave form morphology were identified in the cethromycin group compared to placebo.

The validity of the trial was demonstrated by the fact that the moxifloxacin positive control group exhibited the expected small change in QT_C duration and that the placebo group's change from baseline was within 2 msec for QT_CI, providing solid evidence demonstrating that the spontaneous factors for QT_C change were well controlled.

8.10.2 Pooled Analyses of Studies

In the analyses of ECG parameters, notable differences for possibly clinically significant values and shifts from baseline are defined as those events that have at least a 2.0 percentage point difference and at least a doubling of incidence between the treatment groups being compared.

The definitions of possibly clinically significant ECG values are presented in Table 63.

Table 63: Possibly Clinically Significant Electrocardiogram Values

Electrocardiogram Variable	Direction	Criterion
Heart rate	Decrease	Decrease of more than 20% to a value <50 bpm
	Increase	Increase of more than 20% to a value >110 bpm
PR Interval	Decrease	Decrease of more than 25%
	Increase	Increase of more than 25%
QRS Interval	Decrease	Decrease of more than 25%
	Increase	Increase of more than 25%
QT_C Interval	Prolonged	Male: value >450 msec Female: value >470 msec
	Very High	Value >500 msec or an increase of >60 msec

8.10.2.1. All Phase I Studies Combined

In the Phase I studies combined, no notable differences were observed between all cethromycin-treated subjects and subjects who received placebo for the incidences of possibly clinically significant ECG values. However, a notable difference was observed between all cethromycin-treated subjects and subjects who received active controls for the incidence of possibly clinically significant decreases in heart rate, which was higher in all cethromycin-treated subjects (2.0%) compared to subjects who received active controls (0%). The incidences of possibly clinically significant ECGs values were similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD. None of the episodes that met the possibly clinically significant criteria for prolonged or very high QT_C interval were reported as treatment-emergent serious adverse events or resulted in discontinuation.

8.10.2.2. All Phase II/III Studies Combined

In the Phase II/III studies combined, no notable differences were observed for the incidences of possibly clinically significant ECG values between all cethromycin-treated subjects and subjects who received active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant ECG values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD. In the Phase II/III studies combined, none of the episodes that met the possibly clinically significant criteria for prolonged or very high QT_C interval were reported as treatment-emergent serious adverse events or resulted in discontinuation.

In the Phase II/III studies combined, the incidences of treatment-emergent possibly clinically significant ECG values were similar among the cethromycin dose groups (<300 mg TDD, 300 mg TDD, 300 mg QD, and >300 mg TDD) for increases and decreases in heart rate, decreases in PR intervals, and prolonged QT_C (Bazett and Fridericia). The incidences of increases in PR intervals and increases and decreases in QRS intervals tended to decrease with increasing dose, with notably higher values for subjects who received cethromycin <300 mg TDD (7.43%, 9.05%, and 4.46%, respectively) compared to those who received the higher doses (300 mg QD: 3.21%, 4.58%, and 2.14%; >300 mg TDD: 1.89%, 1.89% and 0.63%, respectively). Although the incidence of prolonged QT_C was generally similar among the cethromycin dose groups, the incidences of very high QT_C intervals (Bazett and Fridericia) were notably higher in the cethromycin >300 mg TDD group (5.03% and 4.4%, respectively) compared with the lower doses (300 mg QD: 1.68% and 1.98%; <300 mg TDD: 2.33% and 2.05%, respectively).

8.11. Topics of Special Interest

Given the observed effects of telithromycin, particular attention was given to the analyses of safety data relevant to the following:

- Hepatotoxicity
- Visual disturbances
- Loss of consciousness
- Exacerbations of myasthenia gravis.

The treatment-emergent adverse event database was searched for any events that appeared under the terms listed in Appendix B.1, including all lower levels contained under the specified term. This broad and all-inclusive analysis was conducted to ensure that adverse events that may be associated with a special interest topic were thoroughly investigated for any possibly linkage to a more complex and serious clinical outcome.

The tabulations presented do not confirm or refute a possible association; rather, they present the incidence of all events based solely on the search terminology.

8.11.1 Exploratory Analyses to Investigate Any Potential Association with Hepatotoxicity

The potential for hepatotoxicity with cethromycin was assessed by a review of treatment-emergent and drug-related, treatment-emergent adverse events potentially associated with hepatotoxicity (see Section 8.11.) and shifts from normal baseline to greatest post-baseline hepatic function values.

8.11.1.1. Hepatic Treatment-Emergent Adverse Events

All Phase I Studies Combined

In the Phase I studies combined, the incidence of treatment-emergent adverse events potentially associated with hepatotoxicity was 1.1% for all cethromycin-treated subjects and 1.2% for subjects who received cethromycin 300 mg QD (Table 66).

Table 64: Treatment-Emergent Adverse Events of Special Interest Potentially Associated with Hepatotoxicity for Selected Treatment Groups (All Phase I Studies)

Search Criteria Preferred Term	Placebo (N=230)	Cethromycin				Active Controls (N=110)
		300 mg TDD (N=637)	300 mg QD (N=505)	≥300 mg QD (N=675)	All Doses (N=1253)	
Subjects with at least 1 TEAE potentially associated with hepatotoxicity	0	8 (1.3)	6 (1.2)	7 (1.0)	14 (1.1)	0
ALT Increased	0	3 (0.5)	3 (0.6)	4 (0.6)	7 (0.6)	0
GGT Increased	0	3 (0.5)	3 (0.6)	3 (0.4)	4 (0.3)	0
Hepatic Enzyme Increased	0	2 (0.3)	0	0	4 (0.3)	0
5' nucleotide Increased	0	2 (0.3)	2 (0.4)	2 (0.3)	3 (0.2)	0
AST Increased	0	2 (0.3)	2 (0.4)	2 (0.3)	3 (0.2)	0
Leucine Aminopeptidase Increased	0	3 (0.5)	3 (0.6)	3 (0.4)	3 (0.2)	0
Ascites	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)	0
Blood Bilirubin Increased	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)	0
Hepatic Cirrhosis	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)	0
Transaminase Increased	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)	0
Subjects with at least 1 drug-related TEAE potentially associated with hepatotoxicity	0	7 (1.1)	5 (1.0)	6 (0.9)	13 (1.0)	0
ALT Increased	0	3 (0.5)	3 (0.6)	4 (0.6)	7 (0.6)	0
GGT Increased	0	3 (0.5)	3 (0.6)	3 (0.4)	4 (0.3)	0
Hepatic Enzyme Increased	0	2 (0.3)	0	0	4 (0.3)	0
5' nucleotide Increased	0	2 (0.3)	2 (0.4)	2 (0.3)	3 (0.2)	0
AST Increased	0	2 (0.3)	2 (0.4)	2 (0.3)	3 (0.2)	0
Leucine Aminopeptidase Increased	0	3 (0.5)	3 (0.6)	3 (0.4)	3 (0.2)	0
Blood Bilirubin Increased	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)	0
Transaminase Increased	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)	0

mg=milligrams; TDD=total daily dose; QD=once daily; TEAE=treatment-emergent adverse event; ALT=alanine aminotransferase; GGT=gamma glutamyltransferase; AST=aspartate aminotransferase
Note: Percentages are displayed in parentheses.

All Phase II/III Studies Combined

In the Phase II/III studies combined, the incidence of treatment-emergent adverse events potentially associated with hepatotoxicity was similar between all cethromycin-treated subjects, cethromycin 300 mg QD subjects, and active control subjects (2.8%, 3.7%, and 2.4%, respectively). Among all cethromycin-treated subjects, the only specific treatment-emergent adverse event potentially associated with hepatotoxicity experienced by ≥1% of subjects was hepatic enzyme increased (1.3%), which was similar to that observed in the active control group (0.9%). Among subjects who received cethromycin 300 mg QD, specific treatment-emergent adverse events potentially associated with hepatotoxicity experienced by ≥1% of subjects were hepatic enzyme increased (1.0%) and ALT increased (1.3%), which are similar in comparison to active controls (0.9% and 0.7%, respectively). A summary of treatment-emergent adverse events of special interest potentially associated with hepatotoxicity for selected treatment groups in all Phase II/III studies combined is presented in Table 65.

Table 65: Treatment-Emergent Adverse Events of Special Interest Potentially Associated with Hepatotoxicity for Selected Treatment Groups (All Phase II/III Studies)

Search Criteria Preferred Term	Cethromycin				Active Controls (N=1611)
	300 mg TDD (N=1558)	300 mg QD (N=870)	≥300 mg QD (N=1188)	All Doses (N=3836)	
Subjects with at least 1 TEAE potentially associated with hepatotoxicity	50 (3.2)	32 (3.7)	43 (3.6)	109 (2.8)	38 (2.4)
Hepatic Enzyme Increased	18 (1.2)	9 (1.0)	14 (1.2)	48 (1.3)	15 (0.9)
ALT Increased	13 (0.8)	11 (1.3)	14 (1.2)	25 (0.7)	11 (0.7)
GGT Increased	7 (0.4)	6 (0.7)	10 (0.8)	16 (0.4)	3 (0.2)
AST Increased	7 (0.4)	6 (0.7)	6 (0.5)	9 (0.2)	5 (0.3)
Blood Bilirubin Increased	0	0	1 (0.1)	4 (0.1)	0
Hepatitis C	1 (0.1)	0	0	3 (0.1)	4 (0.2)
Hepatitis Toxic	3 (0.2)	3 (0.3)	3 (0.3)	3 (0.1)	0
Hyperbilirubinaemia	1 (0.1)	0	0	3 (0.1)	0
Transaminases Increased	3 (0.2)	2 (0.2)	2 (0.2)	3 (0.1)	1 (0.1)
Cholelithiasis	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)	0
Hepatitis	2 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)	0
Liver Function Test Abnormal	0	0	0	2 (0.1)	2 (0.1)
Cholestasis	0	0	0	1 (<0.1)	1 (0.1)
Gallbladder Disorder	0	0	0	1 (<0.1)	0
Hepatic Enzyme Abnormal	1 (0.1)	0	0	1 (<0.1)	0
Hepatic Function Abnormal	0	0	0	1 (<0.1)	1 (0.1)
Hepatic Steatosis	1 (0.1)	0	0	1 (<0.1)	0
Hepatitis Viral	1 (0.1)	1 (0.1)	1 (0.1)	1 (<0.1)	0
Hepatomegaly	1 (0.1)	0	0	1 (<0.1)	0
Hepatitis Cholestatic	0	0	0	0	1 (0.1)
Portal Hypertension	0	0	0	0	1 (0.1)
Varices Oesophageal	0	0	0	0	1 (0.1)

mg=milligrams; TDD=total daily dose; QD=once daily; TEAE=treatment-emergent adverse event; ALT=alanine aminotransferase; GGT=gamma glutamyl transferase; AST=aspartate aminotransferase
Note: Percentages are displayed in parentheses.

8.11.1.2. Shifts from Baseline in Hepatic Function Tests

All Phase I Studies Combined

In the Phase I studies combined, asymptomatic and reversible shifts from normal baseline to above the ULN in hepatic function tests were observed. The maximum shift for the majority of these subjects was less than 2X ULN.

The incidences of shifts from normal baseline hepatic function tests including ALT, AST, alkaline phosphatase, GGT, and total bilirubin to elevations ≥3 × ULN and ≥5 × ULN were all <1% among all cethromycin-treated subjects. Among subjects with normal values at baseline, one placebo subject had a post-baseline ALT value ≥3 × ULN; no subjects who received active controls had post-baseline hepatic function test values ≥3 × ULN. The incidences of shifts from normal baseline to elevations in hepatic function tests ≥3 × ULN or ≥5 × ULN were similar among all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD. A summary of shifts from normal baseline to the greatest value above the ULN in post-baseline

hepatic function values in all Phase I studies combined is presented for selected treatment groups in Table 66.

Table 66: Shifts From Normal Baseline to >1 x ULN, ≥2 x ULN, ≥3 × ULN and ≥5 × ULN in Post-Baseline Hepatic Function Values for Selected Treatment Groups (All Phase I Studies)

Variable	Placebo (N=230)	Cethromycin				Active Controls (N=110)
		300 mg TDD (N=637)	300 mg QD (N=505)	≥300 mg QD (N=675)	All Doses (N=1253)	
ALT (U/L)						
>1 x ULN	11 (0.5)	55 (8.6)	41 (8.1)	65 (9.6)	103 (8.2)	1 (0.9)
≥2 x ULN	2 (0.9)	10 (1.6)	8 (1.6)	10 (1.5)	17 (1.4)	0
≥3 × ULN	1 (0.4)	6 (0.9)	4 (0.8)	5 (0.7)	10 (0.8)	0 (0.0)
≥5 × ULN	0 (0.0)	3 (0.5)	2 (0.4)	2 (0.3)	5 (0.4)	0 (0.0)
AST (U/L)						
>1 x ULN	4 (1.7)	30 (4.7)	24 (4.8)	28 (4.1)	56 (4.5)	0 (0.0)
≥2 x ULN	1 (.4)	8 (1.3)	6 (1.2)	6 (0.8)	12 (1.0)	0 (0.0)
≥3 × ULN	0 (0.0)	3 (0.5)	2 (0.4)	2 (0.3)	6 (0.5)	0 (0.0)
≥5 × ULN	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)
GGT (U/L)						
>1 x ULN	6 (2.6)	15 (2.4)	12 (2.4)	13 (1.9)	26 (2.1)	0 (0.0)
≥2 x ULN	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	4 (0.3)	0 (0.0)
≥3 × ULN	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)
≥5 × ULN	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Total Bilirubin (µmol/L)						
>1 x ULN	8 (3.5)	35 (5.5)	29 (5.7)	35 (5.2)	54 (4.3)	7 (6.4)
≥2 x ULN	0 (0.0)	5 (0.8)	4 (0.8)	4 (0.6)	5 (0.4)	0 (0.0)
≥3 × ULN	0 (0.0)	3 (0.5)	2 (0.4)	2 (0.3)	3 (0.2)	0 (0.0)
≥5 × ULN	0 (0.0)	3 (0.5)	2 (0.4)	2 (0.3)	3 (0.2)	0 (0.0)

mg=milligrams; TDD=total daily dose; QD=once daily; ULN=upper limit of normal; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase

All Phase II/III Studies Combined

In the Phase II/III studies combined, asymptomatic and reversible shifts in hepatic function tests from normal baseline to above the ULN were observed. The maximum shift for the majority of subjects with normal baseline values was less than 2X ULN. However, the shifts appear to occur with greater frequency in Phase II/III subjects when compared to data from Phase I normal healthy subjects, perhaps as the result of an uncharacterized relationship between liver function test abnormalities and the infectious process. Exploratory analyses conducted by the sponsor could establish no relationship to concomitant medication use or other comorbid diseases among the Phase II/III subjects with elevated hepatic function tests.

The incidences of shifts from normal baseline hepatic function tests to elevations ≥3 × ULN and ≥5 × ULN were <1% among all cethromycin-treated subjects and subjects who received active

controls. The incidences of shifts from normal baseline to elevations in hepatic function tests ≥3 × ULN or ≥5 × ULN were similar among all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD. A summary of shifts from normal baseline to the greatest value above the ULN in post-baseline hepatic function values in all Phase II/III studies combined is presented for selected treatment groups in Table 67.

Table 67: Shifts From Normal Baseline to >1 x ULN, ≥2 x ULN, ≥3 × ULN and ≥5 × ULN in Post-Baseline Hepatic Function Values for Selected Treatment Groups (All Phase II/III Studies)

Variable	Cethromycin				Active Controls (N=1611)
	300 mg TDD (N=1558)	300 mg QD (N=870)	≥300 mg QD (N=1188)	All Doses (N=3836)	
ALT (U/L)					
>1 x ULN	200 (12.8)	127 (14.6)	166 (14.0)	410 (10.7)	143 (8.9)
≥2 x ULN	31 (2.0)	26 (3.0)	29 (2.4)	55 (1.4)	21 (1.3)
≥3 × ULN	7 (0.4)	7 (0.8)	8 (0.7)	14 (0.4)	1 (<0.1)
≥5 × ULN	2 (0.1)	2 (0.2)	2 (0.2)	5 (0.1)	0 (0.0)
AST (U/L)					
>1 x ULN	131 (8.4)	88 (10.1)	119 (10.0)	296 (7.7)	103 (6.4)
≥2 x ULN	22 (1.4)	15 (1.7)	16 (1.3)	33 (0.9)	8 (0.5)
≥3 × ULN	10 (0.6)	7 (0.8)	8 (0.7)	19 (0.5)	1 (<0.1)
≥5 × ULN	4 (0.3)	3 (0.3)	4 (0.3)	10 (0.3)	0 (0.0)
GGT (U/L)					
>1 x ULN	68(4.4)	47 (5.4)	59 (5.0)	165 (4.3)	66 (4.1)
≥2 x ULN	11 (0.7)	9 (1.0)	13 (1.1)	29 (0.8)	5 (0.3)
≥3 × ULN	3 (0.2)	2 (0.2)	4 (0.3)	11 (0.3)	3 (0.2)
≥5 × ULN	2 (0.1)	1 (0.1)	1 (0.1)	3 (<0.1)	1 (0.1)
Total Bilirubin (µmol/L)					
>1 x ULN	33 (2.1)	13 (1.5)	18 (1.5)	83 (2.2)	16 (1.0)
≥2 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
≥3 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥5 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

mg=milligrams; TDD=total daily dose; QD=once daily; ULN=upper limit of normal; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase

8.11.1.3. Serious Hepatic Events Associated with Telithromycin

Telithromycin has been associated with reports of serious events of hepatotoxicity such as manifestations of Hy's law, fulminant liver failure, liver biopsy, liver transplant, and jaundice have been documented.

No similar events have been identified in the cethromycin clinical program.

In addition, a recent publication by Brinker *et al*. has reported the identification of a possible clinical presentation of signs and symptoms that were associated with telithromycin-induced drug injury.[50] This presentation is characterized by the short time of onset of symptoms, which include fever, abdominal pain, jaundice, and, in some cases, ascites.

In the cethromycin clinical program, no subjects presented with this combination of symptoms

8.11.1.4. Narratives

The majority of the subjects that had treatment-emergent adverse events potentially associated with hepatotoxicity or elevated liver function tests had an alternative etiology specified or the event was noted to have resolved upon follow-up. However, across all studies and phases, 12 cethromycin subjects and 1 active control subject experienced treatment-emergent adverse events for which follow up to resolution was not documented or no alternate etiology was specified. Brief narratives are presented for each of these subjects in Appendix B.2.

8.11.2 Exploratory Analyses to Investigate Any Potential Associations with Visual Disturbances

The method for evaluating adverse events related to visual disturbances is summarized in Section 8.11.

8.11.2.1. All Phase I Studies Combined

In the Phase I studies combined, the incidence of treatment-emergent adverse events potentially associated with visual disturbances was similar among cethromycin, placebo, and active control treated subjects (0.3%, 0.9%, and 0%, respectively). In the cethromycin group, the event was only observed among subjects who received doses >300 mg. Two of these events occurred in subjects receiving 900 mg QD, three times the targeted dose for CAP. No subject in Phase I experienced an event at the targeted therapeutic dose of 300 mg. A summary of treatment-emergent adverse events of special interest potentially associated with visual disturbances for selected treatment groups in all Phase I studies combined is presented in Table 68.

Table 68: Treatment-Emergent Adverse Events of Special Interest Potentially Associated with Visual Disturbances for Selected Treatment Groups (All Phase I Studies)

Search Criteria Preferred Term	Placebo (N=230)	Cethromycin				Active Controls (N=110)
		300 mg TDD (N=637)	300 mg QD (N=505)	≥300 mg QD (N=675)	All Doses (N=1253)	
Subjects with at least 1 TEAE potentially associated with visual disturbance	2 (0.9)	0	0	3 (0.4)	4 (0.3)	0
Vision Blurred	0	0	0	1 (0.1)	2 (0.2)	0
Diplopia	0	0	0	1 (0.1)	1 (0.1)	0
Visual Disturbance	2 (0.9)	0	0	1 (0.1)	1 (0.1)	0

mg=milligrams; TDD=total daily dose; QD=once daily; TEAE=treatment-emergent adverse event
Note: Percentages are displayed in parentheses.

8.11.2.2. All Phase II/III Studies Combined

In the Phase II/III studies combined, the incidence of treatment-emergent adverse events potentially associated with visual disturbances was 0.2% for all cethromycin-treated subjects and 0.1% for subjects who received cethromycin 300 mg QD. The sole subject reporting blurred vision in the 300 mg group described the event as occurring daily for 30 minutes after taking the matching placebo dose only. None of the subjects who received active controls experienced these types of events. Each of the specific treatment-emergent adverse events potentially

associated with visual disturbances was experienced by ≤0.1% of all cethromycin-treated subjects. A summary of treatment-emergent adverse events of special interest potentially associated with visual disturbances for selected treatment groups in all Phase II/III studies combined is presented in Table 69.

Table 69: Treatment-Emergent Adverse Events of Special Interest Potentially Associated with Visual Disturbances for Selected Treatment Groups (All Phase II/III Studies)

Search Criteria Preferred Term	Cethromycin				Active Controls (N=1611)
	300 mg TDD (N=1558)	300 mg QD (N=870)	≥300 mg QD (N=1188)	All Doses (N=3836)	
Subjects with at least 1 TEAE potentially associated with visual disturbance	1 (0.1)	1 (0.1)	2 (0.2)	6 (0.2)	0
Vision Blurred	1 (0.1)	1 (0.1)	2 (0.2)	4 (0.1)	0
Diplopia	0	0	0	1 (<0.1)	0
Visual Disturbance	0	0	0	1 (<0.1)	0

mg=milligrams; TDD=total daily dose; QD=once daily; TEAE=treatment-emergent adverse event
Note: Percentages are displayed in parentheses.

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8.11.3 Exploratory Analyses to Investigate Any Potential Association with Loss of Consciousness

The method for evaluating adverse events related to loss of consciousness is summarized in Section 8.11.

8.11.3.1. All Phase I Studies Combined

In the Phase I studies combined, the incidence of treatment-emergent adverse events potentially associated with loss of consciousness was 1.3% for all cethromycin-treated subjects and 0.2% for subjects who received cethromycin 300 mg QD. None of the subjects who received placebo or active controls experienced these types of events. Among all cethromycin-treated subjects, the only specific treatment-emergent adverse event potentially associated with loss of consciousness experienced by ≥1% of subjects was syncope vasovagal (12 subjects; 1.0%); all of these events were documented as being associated with venipuncture. A summary of treatment-emergent adverse events of special interest potentially associated with loss of consciousness for selected treatment groups in all Phase I studies combined is presented in Table 70.

Table 70: Treatment-Emergent Adverse Events of Special Interest Potentially Associated with Loss of Consciousness for Selected Treatment Groups (All Phase I Studies)

Search Criteria Preferred Term	Placebo (N=230)	Cethromycin				Active Controls (N=110)
		300 mg TDD (N=637)	300 mg QD (N=505)	≥300 mg QD (N=675)	All Doses (N=1253)	
Subjects with at least 1 TEAE potentially associated with loss of consciousness	0	2 (0.3)	1 (0.2)	6 (0.9)	16 (1.3)	0
Syncope Vasovagal	0	2 (0.3)	1 (0.2)	4 (0.6)	12 (1.0)	0
Syncope	0	0	0	2 (0.3)	5 (0.4)	0

mg=milligrams; TDD=total daily dose; QD=once daily; TEAE=treatment-emergent adverse event
Note: Percentages are displayed in parentheses.

8.11.3.2. All Phase II/III Studies Combined

In the Phase II/III studies combined, the incidence of treatment-emergent adverse events potentially associated with loss of consciousness was similar between all cethromycin-treated subjects (0.2%) and subjects who received active controls (0.2%). None of the subjects who received cethromycin 300 mg QD experienced these types of events. Each of the specific treatment-emergent adverse events potentially associated with loss of consciousness was experienced by ≤0.1% of all cethromycin-treated subjects. A summary of treatment-emergent adverse events of special interest potentially associated with loss of consciousness for selected treatment groups in all Phase II/III studies combined is presented in Table 71.

Table 71: Treatment-Emergent Adverse Events of Special Interest Potentially Associated with Loss of Consciousness for Selected Treatment Groups (All Phase II/III Studies)

Search Criteria Preferred Term	Cethromycin				Active Controls (N=1611)
	300 mg TDD (N=1558)	300 mg QD (N=870)	≥300 mg QD (N=1188)	All Doses (N=3836)	
Subjects with at least 1 TEAE potentially associated with loss of consciousness	4 (0.3)	0	1 (0.1)	7 (0.2)	3 (0.2)
Syncope	1 (0.1)	0	1 (0.1)	3 (0.1)	0
Syncope Vasovagal	1 (0.1)	0	0	2 (0.1)	0
Loss of Consciousness	1 (0.1)	0	0	1 (<0.1)	0
Ventricular Extrasystoles	1 (0.1)	0	0	1 (<0.1)	3 (0.2)

mg=milligrams; TDD=total daily dose; QD=once daily; TEAE=treatment-emergent adverse event
Note: Percentages are displayed in parentheses.

8.11.4 Exploratory Analyses to Investigate Any Potential to Exacerbate Myasthenia Gravis

The method for evaluating adverse events related to potential exacerbations of myasthenia gravis is summarized in Section 8.11.

8.11.4.1. All Phase I Studies Combined

In the Phase I studies combined, the incidence of treatment-emergent adverse events potentially associated with exacerbation of myasthenia gravis, which also included events of visual

disturbance previously presented in Section 8.11.2.1, was similar for all cethromycin treated, cethromycin 300 mg QD, placebo, and active control subjects (0.8%, 0.6%, 0.9%, and 0%, respectively). Each of the specific treatment-emergent adverse events potentially associated with exacerbation of myasthenia gravis was experienced by ≤0.2% of all cethromycin-treated subjects. A summary of treatment-emergent adverse events of special interest potentially associated with exacerbation of myasthenia gravis for selected treatment groups in all Phase I studies combined is presented in Table 72.

Table 72: Treatment-Emergent Adverse Events of Special Interest Potentially Associated with Exacerbation of Myasthenia Gravis for Selected Treatment Groups (All Phase I Studies)

Search Criteria Preferred Term	Placebo (N=230)	Cethromycin				Active Controls (N=110)
		300 mg TDD (N=637)	300 mg QD (N=505)	≥300 mg QD (N=675)	All Doses (N=1253)	
Subjects with at least 1 TEAE potentially associated with exacerbation of myasthenia gravis	2 (0.9)	3 (0.5)	3 (0.6)	8 (1.2)	10 (0.8)	0
Vision Blurred	0	0	0	1 (0.1)	2 (0.2)	0
Diplopia	0	0	0	1 (0.1)	1 (0.1)	0
Muscle Spasms	0	1 (0.2)	1 (0.2)	2 (0.3)	3 (0.2)	0
Muscle Twitching	0	1 (0.2)	1 (0.2)	1 (0.1)	2 (0.2)	0
Muscle Tightness	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)	0
Muscular Weakness	0	0	0	1 (0.1)	1 (0.1)	0
Visual Disturbance	2 (0.9)	0	0	1 (0.1)	1 (0.1)	0

mg=milligrams; TDD=total daily dose; QD=once daily; TEAE=treatment-emergent adverse event
Note: Percentages are displayed in parentheses.

8.11.4.2. All Phase II/III Studies Combined

In the Phase II/III studies combined, the incidence of treatment-emergent adverse events potentially associated with exacerbation of myasthenia gravis was similar between all cethromycin-treated subjects, 300 mg QD cethromycin treated subject, and active controls (0.8%, 1.0%, 0.6%, respectively). Each of the specific treatment-emergent adverse events potentially associated with exacerbation of myasthenia gravis was experienced by ≤0.4% of all cethromycin-treated subjects. A summary of treatment-emergent adverse events of special interest potentially associated with exacerbation of myasthenia gravis for selected treatment groups in all Phase II/III studies combined is presented in Table 73.

Table 73: Treatment-Emergent Adverse Events of Special Interest Potentially Associated with Exacerbation of Myasthenia Gravis for Selected Treatment Groups (All Phase II/III Studies)

Search Criteria Preferred Term	Cethromycin				Active Controls (N=1611)
	300 mg TDD (N=1558)	300 mg QD (N=870)	≥300 mg QD (N=1188)	All Doses (N=3836)	
Subjects with at least 1 TEAE potentially associated with exacerbation of myasthenia gravis	13 (0.8)	9 (1.0)	13 (1.1)	31 (0.8)	10 (0.6)
Vision Blurred	1 (0.1)	1 (0.1)	2 (0.2)	4 (0.1)	0
Diplopia	0	0	0	1 (<0.1)	0
Muscle Spasms	7 (0.4)	3 (0.3)	5 (0.4)	16 (0.4)	5 (0.3)
Dysphonia	2 (0.1)	2 (0.2)	2 (0.2)	3 (0.1)	1 (0.1)
Muscular Weakness	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)	0
Respiratory Failure	1 (0.1)	1 (0.1)	2 (0.2)	2 (0.1)	0
Muscle Fatigue	0	0	0	1 (<0.1)	0
Visual Disturbance	0	0	0	1 (<0.1)	0
Myosclerosis	1 (0.1)	1 (0.1)	1 (0.1)	1 (<0.1)	0
Dysphagia	0	0	0	0	1 (0.1)
Muscle Haemorrhage	0	0	0	0	1 (0.1)
Muscle Tightness	0	0	0	0	1 (0.1)
Sensation of Heaviness	0	0	0	0	1 (0.1)

mg=milligrams; TDD=total daily dose; QD=once daily; TEAE=treatment-emergent adverse event
Note: Percentages are displayed in parentheses.

8.11.5 Differences Among Subpopulations

Results of Phase I studies indicate no difference in pharmacokinetic profile between Japanese and non-Japanese subjects and that no dose adjustment is required when cethromycin is administered to subjects with mild or moderate hepatic impairment or to subjects with severe renal impairment.

In the two Phase III controlled CAP studies combined, the treatment-emergent adverse event profile of cethromycin was consistent across demographic characteristics including gender, race, age, and Fine criteria. Additionally, no clinically important differences were observed between the cethromycin and clarithromycin groups when the incidences of possibly clinically significant laboratory values were analyzed by gender and age. A history of cardiac disease, hepatic disease, or diabetes had no clinically important effect on the treatment-emergent adverse event profile of cethromycin.

In the two Phase III controlled CAP studies combined, the treatment-emergent adverse event profile of cethromycin was consistent across regions, alcohol use, and tobacco use.

8.12. Safety Conclusions

- Safety data from a total of 5089 subjects have demonstrated that cethromycin is safe and well tolerated.
- The most commonly reported adverse events were dysgeusia, diarrhea, nausea and headache.
- The incidences of deaths, treatment-emergent serious adverse events and events that resulted in discontinuation were low and similar between all cethromycin-treated subjects and subjects who received active controls.
- A Phase I thorough QT study showed no signal of any effect of cethromycin on AV conduction, depolarization, or cardiac repolarization as measured by the PR, QRS, QTcI, or QTcF interval durations at the 300 mg therapeutic dose.
- The significant safety events of hepatotoxicity, visual disturbances, loss of consciousness, and exacerbation of myasthenia gravis observed with telithromycin were not observed in the cethromycin clinical program.
- Phase I studies demonstrate no dose adjustment is required when cethromycin is administered to subjects with mild or moderate hepatic impairment or to subjects with severe renal impairment.

It is concluded that cethromycin, dosed at 300 mg QD, has demonstrated an acceptable safety profile for use in the treatment of CAP in patients 18 years of age and above.

9. BENEFIT RISK

Community-acquired pneumonia remains a challenging health care issue. Emerging bacterial resistance to the current armamentarium of anti-CAP agents, especially the emergence of macrolide-resistant *S. pneumoniae*, makes the choice of treatment agents challenging. Additionally, bacterial resistance is an ever evolving problem, and new agents currently under development today may play an even greater role in the future treatment of CAP. Currently available agents are well on their way to either losing efficacy in the eradication of CAP-causative pathogens, or joining the ever expanding group of antibacterial agents with serious safety issues, limiting their clinical uses.

Cethromycin, a novel ketolide agent, appears to address these issues by offering adequate pathogen coverage for the treatment of mild to moderate CAP, while providing a safety profile which appears to be void of some of the more serious adverse events seen in treatment with other ketolide or quinolone agents. While the number of exposures to cethromycin is obviously lower than exposures to marketed products, the absence of serious safety signals seen to date is reassuring.

The antibacterial activity of cethromycin is mediated through binding to the bacterial target, the 23S rRNA of the 50S subunit of the ribosome. Macrolide agents share this target; however, they have fewer contact points and lower binding affinity. Resistance to macrolide agents is often through methylation of the macrolide contact site resulting in an inability to bind to the target. By virtue of additional contact points, cethromycin is able to overcome this methylation-mediated resistance mechanism. In addition, the enhanced binding affinity of cethromycin to its molecular target is helpful in overcoming bacterial resistance mediated via an efflux mechanism and also results in marked increases in antibacterial activity when compared to both macrolide agents and the marketed ketolide agent telithromycin. Cethromycin retains activity against clinical isolates of telithromycin-resistant *S. pneumoniae*, a phenomenon believed to be the result of the enhanced binding kinetics of cethromycin.

Fluoroquinolone agents, such as levofloxacin and moxifloxacin, also provide adequate coverage against both susceptible- and macrolide-resistant CAP-causative pathogens. Unfortunately, the antibacterial coverage of these agents extends beyond common CAP-causative pathogens, resulting in the eradication of other bacterial species present in non-target sites such as the gut. The destruction of these enteric Gram-negative bacteria allows for an overgrowth of other damaging bacterial species, such as *C. difficile*, resulting in serious side effects to treatment such as pseudomembranous colitis. This potentially fatal complication is becoming a larger issue as quinolone antibiotic use continues to increase. The limited activity of cethromycin against enteric Gram-negative bacteria should limit the collateral damage often seen with quinolone treatment, yet preserve the favorable activity against susceptible and resistant CAP-causative pathogens.

CAP is treated empirically and, thus, coverage of likely causative pathogens is essential for a new anti-CAP agent. In addition to the common CAP-causative pathogens *S. pneumoniae, H. influenzae, S. aureus,* and *M. catarrhalis* and the atypical CAP-causative pathogens *C. pneumoniae, M. pneumoniae,* and *L. pneumophila*, new potential pathogens or resistant forms of the above pathogens continue to emerge. Cethromycin has also demonstrated activity against

the USA300 strain of community-acquired MRSA. This activity may have increased importance in the future as treatment providers attempt to empirically cover this potential CAP-causative pathogen. The use of the PCV-7 vaccine has resulted in the emergence of a multidrug resistant *S. pneumoniae* strains (19A and 19F) capable of causing severe invasive disease. Initial investigations have demonstrated the potent activity of cethromycin against these strains. These additional activities, while not demonstrated clinically, provide additional evidence for the utility of cethromycin as an empirical agent in the treatment of mild to moderate CAP.

The incidence of bacterial resistance to the marketed ketolide agent telithromycin seen globally has been impressively low. In all clinical studies conducted to date, there have been no demonstrated cases of increased clinical isolate resistance to cethromycin. While it is possible to create resistant bacterial strains with increased MIC values for cethromycin in the laboratory by serial passage techniques, it appears unlikely that resistance to this agent would be swift in developing in the global community. This property, combined with demonstrated activity against all major classes of antibiotic resistance (including telithromycin and fluoroquinolone) argues for the use of cethromycin as a first line treatment for mild to moderate CAP.

Dosing of cethromycin at 300 mg QD results in plasma concentration levels which exceed the MIC_{90} for the majority of CAP-causative pathogens (exception *H. influenzae*). Importantly, however, cethromycin is sequestered at the desired site of action for the treatment of respiratory infections, the pulmonary tissue. Concentrations of cethromycin seen in epithelial lining fluid are ~10-fold higher than those seen in plasma and concentration in alveolar macrophages ~300-fold higher. The terminal half-life of cethromycin is also longer in pulmonary tissue when compared to plasma.

Cethromycin is primarily eliminated by hepatic metabolism involving cytochrome P450 3A-dependent pathways. As a result, concomitant administration of drugs which interact with the CYP3A pathway must be monitored. Several drug-drug interaction studies involving cethromycin have been performed and their results detailed in this submission. The concomitant administration of cethromycin and statin agents has not been examined and, as such, a recommendation is being made to discontinue statin administration for the 7-day cethromycin dosing period. Based on the benign nature of the cethromycin plasma concentration increases observed in controlled Phase III studies, it is unlikely that the effect of a concomitantly administered CYP3A-interacting agent would present issues based on cethromycin plasma concentration increases; however, effects of cethromycin on plasma concentrations of other CYP3A-interacting agents should likely be considered and proper precautions (therapeutic level monitoring, etc.) taken.

Common treatment-emergent adverse events seen with cethromycin dosing are gastrointestinal in nature and include nausea and diarrhea. Incidences of these adverse events in the controlled Phase III CAP studies were similar to or less than those reported in controlled studies of levofloxacin and telithromycin. Importantly, no incidence of severe diarrhea requiring intervention was seen in cethromycin-treated subjects. An increased incidence of dysgeusia or taste perversion was experienced by subjects receiving cethromycin when compared to subjects receiving treatment with other marketed agents (including clarithromycin). This adverse event is transient and resolves upon cessation of dosing.

Laboratory evaluations in subjects receiving cethromycin are generally unremarkable with the exception of incidences of transient liver function test elevation. In all trials performed, transient

increases in these parameters, typically in the 2-3 × ULN range but occasionally >3 × ULN, have been seen. Extended efforts were undertaken to follow these elevations for subjects enrolled in later clinical studies. In all subjects for whom this extended evaluation was possible (i.e., not lost to follow-up) increases have resolved to baseline promptly following cessation of, or even by the conclusion of, dosing. No subjects experiencing these transient elevations were symptomatic of any hepatotoxicity. Importantly, no subjects have experienced simultaneous significant elevation of aminotransferases and bilirubin (Hy's Law).

In addition to the clinical laboratory findings discussed in the previous paragraph, and in contrast to that seen in the telithromycin development program, no symptomatic case of hepatotoxicity was seen in the cethromycin clinical program. Thus, no liver biopsies were performed and no human liver pathology collected in subjects receiving cethromycin. Additionally, the preclinical toxicity profile of cethromycin did not display the same safety signals (hepatic necrosis, hepatocellular hypertrophy, multinucleated hepatocytes) seen in the telithromycin preclinical program. Taken together, this information suggests that the hepatotoxicity issues seen in the telithromycin clinical experience may not be common to other members of the ketolide class. That said, additional conscientious monitoring should be a part of the post-marketing program for cethromycin and every effort should be made to detect relevant safety signals and prevent serious complications if they arise.

Fluoroquinolones, macrolides, and telithromycin have all exhibited the potential to prolong the QT_C interval of the ECG in certain individuals. This may place these individuals at increased risk for ventricular disturbances while taking these drugs. In both the controlled CAP clinical trials recently completed, and the E14-compliant thorough QT study completed in 2007, no signal suggestive of increased QT_C interval in subjects dosed with 300 mg of cethromycin was seen.

Additional safety concerns seen in currently marketed agents include visual disturbances, sudden loss of consciousness, and exacerbation of myasthenia gravis. No similar safety signals appear to be present. However, with increased exposure to the agent, diligence will be undertaken to detect such signals if manifested.

Fluoroquinolones are generally contraindicated for the treatment of pediatric CAP. To date, while a pediatric development plan has not been initiated, no safety signal detected in the adult population appears prohibitive to the development of cethromycin for pediatric CAP.

Black box warnings are currently required on the labels of both telithromycin and levofloxacin due to liver toxicity and tendon rupture, respectively. Each of these marketed drugs demonstrates a bacteriological activity profile similar to cethromycin yet appears to also place individuals receiving these drugs at considerable risk for serious adverse events. Information collected thus far does not support the same type of risk profile with cethromycin.

In all CAP clinical trials completed to date, cethromycin dosed at 300 mg QD has demonstrated a clinical cure rate in per protocol subjects of >90%. Cure rates for the ITT population have ranged between 82% and 84%. When compared to marketed anti-CAP agents, these cure rates are similar to or better than those seen previously. In the two controlled Phase III CAP trials discussed in detail in this submission, cethromycin achieved non-inferiority to the comparator agent clarithromycin, dosed at 250 mg BID, in the per protocol population. In the ITT population, one trial did not meet non-inferiority using a -10% delta for non-inferiority. This

could potentially be attributed to the extraordinary clinical cure rate achieved in the population receiving comparator drug (88.5%). Nevertheless, clinical activity of cethromycin does not appear to be inferior to other marketed agents when measured using clinical cure rates in different population analyses. Similar results were demonstrated in bacterial eradication rates, radiographic response rates, and clinical signs and symptoms resolution rates.

Several smaller sub-analyses are suggestive of additional advantages offered by cethromycin over currently marketed agents. These analyses, while limited in number of individuals examined, nevertheless provide helpful information regarding potential additional applications in the treatment of CAP and are detailed in this submission. Briefly, cethromycin maintained a similar clinical cure rate in the ITT population in subjects infected with macrolide-susceptible strains of *S. pneumoniae* and subjects infected with macrolide-resistant *S. pneumoniae*. This reinforces the *in vitro* activity profile of cethromycin, discussed above, against macrolide-resistant organisms. In a separate analysis, the efficacy of cethromycin in the treatment of subjects with *S. pneumoniae* bacteremia was explored. Treatment with cethromycin resulted in a 77.8% clinical cure rate and an 88.9% bacterial eradication rate in ITT subjects with *S. pneumoniae* bacteremia. Together, these results demonstrate the potential effectiveness of cethromycin in the treatment of two difficult-to-treat populations; those with drug-resistant *S. pneumoniae* infection, and those with *S. pneumoniae* bacteremia.

In conclusion, the medical community is faced with additional challenges in the treatment of mild to moderate CAP. Treatment agents must have the capability to eradicate drug-resistant causative pathogens, including new targets such as the USA300 strain of community-acquired MRSA and the 19A and 19F serotypes of *S. pneumoniae,* in addition to the susceptible strains of the typical pathogens and the atypical or intracellular pathogens. A satisfactory drug must be able to eradicate all of these species yet leave other non-CAP causative species alone, thus prohibiting the overgrowth of harmful bacteria such as *C. difficile* in the gut. This selective antibacterial activity must coexist with a tolerable and benign safety profile, something which has become more and more difficult for an antibacterial agent to achieve in the recent past. Several currently available agents lack the antibacterial activity to address the pathogen challenges facing the CAP treatment provider. While several have the antibacterial activity, this activity comes at the expense of collateral damage and patient safety.

Cethromycin may provide the prescribing community with an agent which retains the antibacterial profile necessary for the treatment of common and more difficult-to-treat CAP, while maintaining an acceptable safety profile, ensuring that the individual receiving the treatment benefits from the treatment. The information presented in this submission supports the use of cethromycin in the treatment of mild-to-moderate CAP due to susceptible strains of *S. pneumoniae, H. influenzae, S. aureus, M. catarrhalis, C. pneumoniae, M. pneumoniae,* or *L. pneumophila* in patients 18 years of age and older. The recommended dose is 300 mg QD for a total of 7 days. The data in the population examined thus far and presented in this submission supports the conclusion that the benefits of cethromycin exceed the risks for the treatment of mild to moderate CAP.

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APPENDIX A: DEATHS

DEATHS: PIVOTAL STUDIES

CL05-001 (Pivotal Phase III Controlled Study in CAP)

Subject 30060089, was a 58-year-old White male with a primary diagnosis of community-acquired pneumonia who started a 7-day treatment with **cethromycin 300 mg QD** on 29AUG2007.

The subject experienced the serious adverse event of severe acute myocardial infarction (acute myocardial infarction) on (b) (6) reported as not related to study medication. Study medication was permanently discontinued due to the event. The subject died on (b) (6).

The subject had a relevant medical history of influenza in 2006, bronchitis in 2004, abdominal hernia repair in 2001, and abdominal lipectomy in 1996. Concomitant medications during the study included Adco-Linctopent (bromhexine hydrochloride, orciprenaline sulfate) and Painagon (codeine phosphate, paracetamol, promethazine hydrochloride).

Subject 20110036, was a 66-year-old White female with a primary diagnosis of community-acquired pneumonia who started a 7-day treatment with **clarithromycin 250 mg BID** on 30MAY2007.

The subject experienced the serious adverse events of moderate lung squamous cell carcinoma stage unspecified (secondary to well differentiated squamous cell carcinoma) and moderate pneumothorax (collapsed left lower lobe lung) on (b) (6) reported as not related to study medication. The subject also experienced the serious adverse event of severe cardiac arrhythmia (cardiac arrhythmia, cardiac arrest) on (b) (6) reported as not related to study medication. The subject died on (b) (6).

The subject had a relevant medical history of hypertension since 1997, hysterectomy in 1980, cholecystectomy in 1985, and chronic obstructive pulmonary disease since 21MAY2003. Concomitant medications during the study included Dyazide (hydrochlorothiazide, triamterene).

Subject 30040013, was a 59-year-old Black male with a primary diagnosis of community-acquired pneumonia who started a 7-day treatment with **clarithromycin 250 mg BID** on 06AUG2007.

The subject experienced the serious adverse event of severe pneumonia (pneumonia) on (b) (6) reported as probably not related to study medication. No action was taken regarding the study medication. The subject died on (b) (6).

The subject had no relevant medical history reported. Concomitant medications during the study included Adco-Linctopent (bromhexine hydrochloride, orciprenaline sulfate) and Cataflam D (diclofenac).

Subject 30060056, was a 79-year-old White female with a primary diagnosis of community-acquired pneumonia who started a 7-day treatment with **clarithromycin 250 mg BID** on 09MAY2007.

The subject experienced the serious adverse event of severe angina pectoris (angina pectoris) on (b) (6) reported as not related to study medication. Study medication was permanently discontinued due to the event. The outcome was reported as not resolved, follow-up not deemed necessary by investigator. The subject also experienced the serious adverse event of severe acute myocardial infarction (acute myocardial infarction) on (b) (6) reported as not related to study medication. The subject died on (b) (6).

The subject had a relevant medical history of chronic obstructive pulmonary disease since 1997, pneumonia from (b) (6) and (b) (6), bleeding peptic ulcer from (b) (6) hysterectomy in 1967, insomnia since 24JAN1997, congestive cardiac failure in from 1997-28FEB2007, ischemic heart disease since 14MAR1997, and cardiomegaly since 22NOV2006. Concomitant medications during the study included Adco-Linctopent (bromhexine hydrochloride, orciprenaline sulfate), Pantoloc (pantoprazole), Pharmapress (enalapril maleate, hydrochlorothiazide), Puresis (furosemide), spironolactone, Stilpane (codeine phosphate, meprobamate, paracetamol), Trepiline (amitriptyline), and Venteze (salbutamol).

CL06-001 (Pivotal Phase III Controlled Study in CAP)

Subject 56060001, was a 52-year-old White non-Hispanic male with a primary diagnosis of community-acquired pneumonia who started a 7-day treatment with **cethromycin 300 mg QD** on 21FEB2007.

The subject experienced the serious adverse events of severe small cell lung cancer stage unspecified (small cell lung cancer stage unspecified) and severe haemoptysis (haemoptysis) on (b) (6) reported as not related to study medication. No action was taken regarding the study medication. The subject died on (b) (6).

The subject had no relevant medical history reported. Concomitant medications during the study included antihaemorrhagics, Euphylong (theophylline), ethylmorphine, and tramadol.

Subject 57040001, was a 71-year-old White non-Hispanic male with a primary diagnosis of community-acquired pneumonia who started a 7-day treatment with **clarithromycin 250 mg BID** on 20DEC2006.

The subject experienced the serious adverse event of severe lung neoplasm malignant (CA of lung) on (b) (6) reported as not related to study medication. Study medication was permanently discontinued. The subject died on (b) (6)

The subject had no relevant medical history reported. Concomitant medications during the study included Enaladex (enalapril maleate), Lopressor (metoprolol tartrate), Rythmex (propafenone hydrochloride), Simovil (simvastatin), and Xalatan (latanoprost).

DEATHS: OTHER STUDIES

Study M00-216 (Phase III Controlled Study in Acute Exacerbations of Chronic Bronchitis)

Subject 20933, an 81-year-old white female assigned to the **azithromycin 500mg QD Day 1/250mg QD Days 2-5** treatment group, was hospitalized for an exacerbation of congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and asthma 4 days after premature discontinuation of study drug, and died 7 days later from a spontaneous rectus abdominis muscle hemorrhage. The subject had a history of COPD/emphysema, asthma, CHF, cor pulmonale, regurgitant mitral valve, aortic stenosis, hypertension, cardiomyopathy, coronary and peripheral arterial disease with stent placement, renal insufficiency, diabetes mellitus, hypothyroidism, polymyalgia rheumatica, and other comorbidities. The subject was receiving multiple concomitant medications including prednisone, aspirin, and diuretic with potassium replacement therapy. On Study Day 1, the subject had elevated BUN and potassium values (COSTART terms: BUN increased and hyperkalemia, respectively) on baseline labs that were thought at the time to be due to renal insufficiency secondary to diuretic use. On Study Day 3, the subject had moderate nausea, diarrhea, and increased fluid retention (COSTART terms: nausea, diarrhea, and congestive heart failure, respectively) and mild black stools and dry mouth (COSTART terms: melena and dry mouth, respectively). The subject was evaluated and revealed that she had discontinued study drug on Study Day 3 and had inadvertently been taking Ceftin that she had at home instead of a diuretic pill. The subject was discontinued from the study, Levaquin therapy was begun, and concomitant medication therapy was adjusted including increases in prednisone and diuretic therapy. The investigator believed the congestive heart failure was probably not related to study drug and due to cor pulmonale, the melena was not related to study drug and due to a GI bleed, and the dry mouth, diarrhea and nausea were possibly related to study drug with alternate etiologies of concomitant diuretic use and GERD, respectively. Upon reevaluation on Study Day 6, the subject condition had improved with the medication readjustment. On Study Day 7, however, the subject had severe increased shortness of breath, fatigue, and fluid retention, diagnosed as exacerbation of asthma, CHF, and COPD (COSTART terms: asthma, heart failure and lung disorder, respectively). These events prompted hospitalization and required medical intervention including intravenous steroid therapy and diuresis. The investigator believed the events were probably not related to study drug, given the subject's prior medical history of these disorders. Although the subject's pulmonary condition improved, the subject had a hemoccult-positive stool and progressive increases in BUN inappropriate to creatinine value rise believed due to an underlying GI bleed with reabsorption. In retrospect, in view of the Study Day 1 BUN elevation, this

was felt in all likelihood to have been present prior to study entry. On Study Day 14, the subject had severe abdominal wall pain and hematoma development, diagnosed as a rectus abdominis muscle bleed (COSTART term: muscle hemorrhage). The subject refused further intervention, received DNR status, and died on Study Day 14. The investigator believed the event was not related to study drug with an alternate etiology of spontaneous rectus hemorrhage.

Subject 20780, a 64-year-old white male assigned to the **azithromycin 500mg QD Day 1/250mg QD Days 2-5** treatment group, experienced an acute exacerbation of COPD (COSTART term: lung disorder) of moderate intensity on Study Day 1. Study drug was prematurely discontinued and the subject was hospitalized for treatment. On Study Day 14, the subject developed moderate supraventricular tachycardia (COSTART term: supraventricular tachycardia). The investigator considered both adverse events to be due to the subject's underlying COPD and not related to study drug. The subject died of respiratory failure/COPD on Study Day 18.

M00-217 ((Phase III Controlled Study in Acute Exacerbations of Chronic Bronchitis)

Subject 21391, a 76-year-old white male assigned to the **cethromycin150 mg QD** treatment group, died on Study Day 4 from acute kidney failure. The subject had a history of several previous episodes of post-renal ureteral obstruction requiring nephrostomy and an ureterointestinal anastamosis since 1983 after a cystectomy for bladder cancer. The subject was hospitalized for urine output failure requiring nephrostomy 8 days before study drug was initiated. The subject then developed ABECB and received study drug for 3 days. Study drug was discontinued due to severe acute urine retention, hydronephrosis, and renal failure (COSTART term: acute kidney failure) that required emergency surgery and was considered life-threatening. Prior to surgery, the subject died on Study Day 4. The investigator considered the adverse event due to hydronephrosis and not related to study drug.

Subject 21188, an 87-year-old white female assigned to the **levofloxacin** 500mg **QD** treatment group, died on Study Day 26 after a myocardial infarction. The subject had a history of hypertension and congestive heart failure. On Study Day 23, 16 days after the final dose of study drug, the subject developed severe chest pain, tachycardia, and dyspnea diagnosed as an anterolateral myocardial infarction (COSTART term: myocardial infarct). The subject was hospitalized for treatment, but died on Study Day 26. The investigator considered the adverse event due to ischemic heart disease and not related to study drug.

M00-219 (Phase III Uncontrolled Study in CAP)

Subject 34086, a 65-year-old male assigned to the **cethromycin 150 mg QD** treatment group, developed severe disorientation, confusion, restlessness, and cyanosis (COSTART term: confusion), severe cyanosis (COSTART term: cyanosis), and severe nervousness (COSTART term: nervousness) on Study Day 4. Study drug was prematurely discontinued, with the final dose having been on Study Day 3. The subject was hospitalized; Atarax, Largactil, and Valium were administered intramuscularly for restlessness and sedation; intramuscular Etomine was administered for confusion; and Ringer's Lactate was administered intravenously for hydration. The investigator considered these adverse events to be due to ischemic heart

disease and coronary thrombosis and not related to study drug. The adverse events lasted 20 hours, until the subject died.

Subject 34045, a 40-year-old male assigned to the **cethromycin 150 mg BID** treatment group, developed worsening pneumonia (COSTART term: pneumonia) on Study Day 11, 7 days after the last dose of study drug. The patient was given Moxypen 500 mg TID for treatment of the pneumonia; however, the patient died on Study Day 12. The investigator considered the pneumonia not related to study drug, with subject refusal of therapy, noncompliance, and bacterial infection as an alternative etiology.

APPENDIX B: ADVERSE EVENTS OF SPECIAL INTEREST

Appendix B.1 Definition of Search Criteria

Given the observed effects of another ketolide agent, particular attention was given to the analyses of safety data relevant to hepatotoxicity, visual disturbances, loss of consciousness, and exacerbation of myasthenia gravis. The treatment-emergent adverse event database was searched for any events that appeared under the terms listed below, including all lower levels contained under the specified term.

Topic of Special Interest	High-Level Group Terms	High-Level Terms/System Organ Classes	Preferred Terms
Adverse events potentially associated with hepatotoxicity	hepatobiliary investigations and hepatobiliary therapeutic procedures	hepatobiliary disorders	
Adverse events potentially associated with visual disturbances	vision disorders		
Adverse events potentially associated with loss of consciousness		disturbances in consciousness NEC (excluding preferred terms of lethargy and somnolence)	
Adverse events potentially associated with exacerbation of myasthenia gravis		myasthenias, muscle tone abnormalities, respiratory failures, muscular autoimmune disorders, neuromuscular junction dysfunction, muscle weakness conditions, muscle related signs and symptoms NEC	pharyngeal hypothaesthesia, diaphragmatic abnormal relaxation, diaphragmatic paralysis, eyelid ptosis, pseudo-blepharoptosis, diplopia, vision blurred, visual disturbance, sensation of heaviness, aphonia, choking, choking sensation, dysphonia, and dysphasia

Appendix B.2 Narratives for Potential Hepatoxicity

Subject 4995-41115, was a 22-year-old male who was randomized to receive **cethromycin 150 mg BID** for 10 days for treatment of sinusitis in Study M00-225. On Day 19, the subject was noted to have increased transaminase (ALT, AST) levels (279 U/L and 206 U/L, respectively). The event was considered severe in intensity and probably related to study drug. The event was non-serious and did not result in discontinuation. No alternative etiology was specified and no past medical history was reported that was relevant to the event. ALT and AST values were 23 U/L and 12 U/L, respectively, at baseline and 38 U/L and 23 U/L, respectively, on Day 12. There was no documented resolution of the elevations as the subject was lost to follow-up with no additional transaminase values reported.

Subject 14024-30402, was a 44-year-old male who was randomized to receive **cethromycin 150 mg BID** for 10 days for treatment of CAP in Study M00-219. On Day 14, the subject was noted to have liver enzyme values (ALT: 336 U/L, AST: 237 U/L, GGT: 221 U/L) that were increased from baseline. The event was considered moderate in intensity and probably not related to study drug. The event was non-serious and did not result in discontinuation. An alternative etiology of viral infection was specified and the subject had a past medical history of hepatitis C. ALT, AST, and GGT values were 63 U/L, 43 U/L, and 140 U/L, respectively, at baseline. As of Day 21, the values were beginning to decrease (194 U/L, 126 U/L, and 238 U/L, respectively); however, the subject refused additional follow up.

Subject 13575-30235, was a 54-year-old female who was randomized to receive **cethromycin 150 mg BID** for 10 days for treatment of CAP in Study M00-219. On Day 4, the subject was noted to have elevated hepatic enzymes (ALT, AST, GGT, and alkaline phosphatase) and was prematurely discontinued from study drug. The event was considered mild in intensity and probably related to study drug. The event was non-serious and no alternative etiology was specified. The subject had a past medical history of asymptomatic elevated liver function tests. Alkaline phosphatase, ALT, AST, and GGT values were 136 U/L, 125 U/L, 129 U/L, and 73 U/L, respectively, at baseline and 185 U/L, 120 U/L, 53 U/L, and 124 U/L, respectively, on Day 4. There was no documented resolution of the elevations as the subject was lost to follow-up.

Subject 12383-3294, was a 27-year-old male who was randomized to receive **cethromycin 300 mg QD** for 7 days for treatment of CAP in Study M99-054. On Day 15, the subject was noted to have increases in ALT and AST. The event was considered mild in intensity and possibly related to study drug. The event was non-serious and did not result in discontinuation. No alternative etiology was specified and no past medical history was reported that was relevant to the event. ALT and AST values were 18 U/L and 21 U/L, respectively, at baseline; 34 U/L and 34 U/L, respectively, on Day 8; and 109 U/L and 223 U/L, respectively, on Day 15. There was no documented resolution of the elevations as the subject was lost to follow-up with no additional transaminase values reported.

Subject 13001-01133, was a 39-year-old male who was randomized to receive **cethromycin 600 mg QD** for 5 days for treatment of acute bacterial exacerbation of chronic bronchitis in Study M99-048. On Day 6, the subject was noted to have an elevated GGT, which was indicated as continuing as of Day 24. The event was considered moderate in intensity and possibly related to study drug. The event was non-serious and did not result in discontinuation. Alternative etiologies of possible undiagnosed gastrointestinal problem, possible hepatitis, and possible alcohol use were specified. No past medical history was reported that was relevant to the event. GGT values were 97 U/L at baseline, 151 U/L on Day 6, 163 U/L on Day 13, 252 U/L on Day 24, and 142 U/L on Day 69. High ALT values were also reported on Day 6 (48 U/L), Day 24 (58 U/L), and Day 69 (45 U/L). In addition, high AST values were reported on Day 6 (41 U/L) and Day 24 (48 U/L). There was no documented resolution of the elevations as no additional liver function test values were reported.

Subject 15626-30344, was a 69-year-old male who was randomized to receive **cethromycin 150 mg QD** for 10 days for treatment of CAP in Study M00-219. On Day 3, the subject was noted to have elevated liver function test values and discontinued study drug. The event was considered moderate in intensity and probably related to study drug. The event was non-serious and no alternative etiology was specified. No past medical history was reported that was relevant to the event. Alkaline phosphatase, ALT, AST, and GGT values were 111 U/L, 55 U/L, 34 U/L, and 86 U/L, respectively, at baseline; 147 U/L, 225 U/L, 181 U/L, and 163 U/L, respectively, on Day 3; 161 U/L, 295 U/L, 171 U/L, and 202 U/L, respectively, on Day 4; and 142 U/L, 125 U/L, 38 U/L, and 186 U/L, respectively, on Day 8. There was no documented resolution of the elevations and no additional liver function test values were reported; however, the investigator noted Day 8 as the end date of the event.

Subject 15014-30697, was a 51-year-old female who was randomized to receive **cethromycin 150 mg QD** for 10 days for treatment of CAP in Study M00-219. On Day 12, the subject was noted to have increased liver function test values, with an unknown outcome. The event was considered mild in intensity and probably related to study drug. The event was non-serious and no alternative etiology was specified. No past medical history was reported that was relevant to the event. ALT and AST values were 15 U/L and 21 U/L, respectively, at baseline; 37 U/L and 39 U/L, respectively, on Day 12; and 54 U/L and 34 U/L, respectively, on Day 22. AST values on Day 37 were 59 U/L and noted as not clinically significant by the investigator. The investigator noted the event as resolved on Day 72. No additional laboratory results were available.

Subject 17264-31003, was a 26-year-old male who was randomized to receive **cethromycin 150 mg BID** for 10 days for treatment of CAP in Study M00-219. On Day 3, the subject was noted to have an elevation in AST with no signs and symptoms. The subject refused follow-up. The event was considered mild in intensity and probably not related to study drug. The event was non-serious and did not result in discontinuation. An alternative etiology of acute inflammation was specified and no past medical history was reported that was relevant to the event. AST values were 14 U/L at baseline and 36 U/L on Day 3. There was no documented resolution of the elevation as no additional values were reported.

Subject 14117-03114, was a 35-year-old female who was randomized to receive **cethromycin 600 mg QD** for 7 days for treatment of CAP in Study M99-054. On Day 4, the subject was noted to have a high GGT value, which was indicated as continuing as of Day 33. The event was considered moderate in intensity and probably not related to study drug. The event was non-serious and did not result in discontinuation. An alternative etiology of alcohol use was specified. No past medical history was reported that was relevant to the event. GGT values were 78 U/L at baseline and 153 U/L on Day 4. In addition, alkaline phosphatase and AST values were 140 U/L and 47 U/L, respectively, on Day 4. There was no documented resolution of the elevations as no additional liver function test values were reported.

Subject 14436-00189, was a 48-year-old female who was randomized to receive **cethromycin 200 mg TID** for 7 days for treatment of acute bacterial exacerbation of chronic bronchitis in Study M98-967. On Day 19, the subject was noted to have a elevated AST, ALT, and alkaline phosphatase levels, which were indicated as continuing as of Day 37. The event was considered severe in intensity and probably related to study drug. The event was non-serious and did not result in discontinuation. No alternative etiology was specified and no past medical history was reported that was relevant to the event. AST, ALT, and alkaline phosphatase values were 11 IU/L, 29 IU/L, and 130 IU/L, respectively, at baseline; 10 IU/L, 15 IU/L, and 131 IU/L, respectively, on Day 5 (on-therapy); 23 IU/L, 12 IU/L, and 212 IU/L, respectively, on Day 9 (first visit off therapy); 1037 IU/L, 297 IU/L, and 343 IU/L, respectively, on Day 19; and 56 IU/L, 59 IU/L, and 215 IU/L, respectively, on Day 37. There was no documented resolution of the elevations beyond Day 37 as the subject refused additional follow-up.

Subject 14507-4202, was a 44-year-old female who was randomized to receive **cethromycin 300 mg QD** for 5 days for treatment of acute bacterial exacerbation of chronic bronchitis in Study M99-048. On Day 13, the subject was noted to have elevated ALT, AST, and GGT values, which were noted to have resolved on Day 19. The event was considered severe in intensity and not related to study drug. The event was non-serious and did not result in discontinuation. No alternative etiology was specified and no past medical history was reported that was relevant to the event. ALT, AST, and GGT values were 15 U/L, 17 U/L, and 4 U/L, respectively, at baseline; 18 U/L, 14 U/L, and 12 U/L, respectively, on Day 7 (first off-therapy visit); 111 U/L, 109 U/L, and 1198 U/L, respectively, on Day 13; and 82 U/L, 58 U/L, and 75 U/L, respectively, on Day 19. In addition, a high alkaline phosphatase value was reported on Day 19 (125 U/L).

Subject 11999-04005, was a 23-year-old male who was randomized to receive **cethromycin 150 mg QD** for 7 days in Study M99-119. On Day 9, the subject was noted to have an increased ALT value, which was indicated as continuing. The event was considered moderate in intensity and probably related to study drug. The event was non-serious and did not result in discontinuation. No alternative etiology was specified and no past medical history was reported that was relevant to the event. ALT values were 26 U/L at baseline and 142 U/L on Day 9. GGT values were elevated at baseline (149 U/L) and on Day 9 (137 U/L). In addition, AST was elevated on Day 9 (64 U/L). There was no documented resolution of the elevations as no additional liver function test values were reported.

Subject 4109-0004, was a 47-year-old female who was randomized to **clarithromycin 250 mg BID** for 7 days for treatment of CAP in Study CL06-001. On Day 4, the subject was reported noted to have an increase in ALT and AST values that did not resolve. The event was considered mild in intensity and probably related to study drug. The event was non-serious and did not result in discontinuation. No alternative etiology was specified and no past medical history was reported that was relevant to the event. ALT and AST values were 24 U/L and 21 U/L, respectively, at baseline; 38 U/L and 57 U/L, respectively, on Day 4; 90 U/L and 68 U/L, respectively, on Day 11; and 84 U/L and 64 U/L, respectively, on Day 17. The investigator noted that the event was not resolved and no additional follow-up was needed. No additional liver function test values were reported.